

12

EUROPEAN PATENT APPLICATION

21 Application number: 90302521.1

51 Int. Cl.⁵: **C07C 401/00, A61K 31/59**

22 Date of filing: 09.03.90

Amended claims in accordance with Rule 86 (2) EPC.

30 Priority: 09.03.89 US 321030
16.02.90 US 481354

43 Date of publication of application:
12.09.90 Bulletin 90/37

84 Designated Contracting States:
AT BE CH DE DK ES FR GB GR IT LI LU NL SE

71 Applicant: **WISCONSIN ALUMNI RESEARCH
FOUNDATION**
614 North Walnut Street
Madison, WI 53705(US)

72 Inventor: **DeLuca, Hector F.**
1809 Highway BB Deerfield
Wisconsin 53531(US)
Inventor: **Schnoes, Heinrich K.**
1806 Summit Avenue
Madison Wisconsin 53705(US)
Inventor: **Perlman, Kato L.**
1 Chippewa Court
Madison Wisconsin 53711(US)
Inventor: **Sicinski, Rafal R.**
University of Warsaw Dept. of Chemistry
02-093 Warsaw Pasteura 1(PL)
Inventor: **Prahl, Jean Martin**
7 Georgetown Court
Madison Wisconsin 53919(US)

74 Representative: **Ellis-Jones, Patrick George**
Armine et al
J.A. KEMP & CO. 14 South Square Gray's Inn
London WC1R 5LX(GB)

54 **19-Nor vitamin D compounds.**

57 This invention provides a novel class of vitamin D-related compounds, namely the 1 α -hydroxy-19-nor-vitamin D analogs, as well as a general method for their chemical synthesis. The compounds exhibit pronounced activity in arresting the proliferation of undifferentiated cells, including malignant cells, and in inducing their differentiation, and thus represent novel therapeutic agents for the treatment of malignant and other diseases characterized by the proliferative growth of undifferentiated cells. Formulations for therapeutic use and treatment methods are also provided.

EP 0 387 077 A1

19-Nor-Vitamin D Compounds

This invention was made with United States government support awarded by the Department of Health and Human Services (NIH), Grant number: DK-14881. The United States Government has certain rights in this invention.

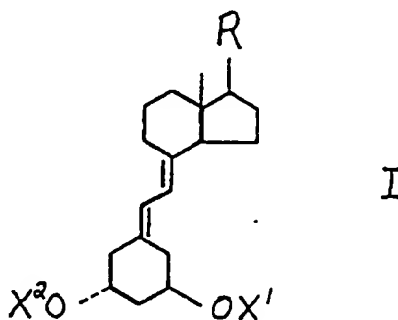
This invention relates to biologically active vitamin D compounds. More specifically, the invention relates to 19-nor-analogs of 1 α -hydroxylated vitamin D compounds and to a general process for their preparation.

Background

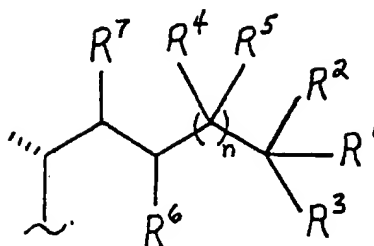
The 1 α -hydroxylated metabolites of vitamin D -- most importantly 1 α ,25-dihydroxyvitamin D₃ and 1 α ,25-dihydroxyvitamin D₂ -- are known as highly potent regulators of calcium homeostasis in animals and humans, and more recently their activity in cellular differentiation has also been established. As a consequence, many structural analogs of these metabolites, such as compounds with different side chain structures, different hydroxylation patterns, or different stereochemistry, have been prepared and tested. Important examples of such analogs are 1 α -hydroxyvitamin D₃, 1 α -hydroxyvitamin D₂, various side chain fluorinated derivatives of 1 α ,25-dihydroxyvitamin D₃, and side chain homologated analogs. Several of these known compounds exhibit highly potent activity *in vivo* or *in vitro*, and possess advantageous activity profiles and thus are in use, or have been proposed for use, in the treatment of a variety of diseases such as renal osteodystrophy, vitamin D-resistant rickets, osteoporosis, psoriasis, and certain malignancies.

Disclosure and Description of the Invention

A class of 1 α -hydroxylated vitamin D compounds not known heretofore are the 19-nor-analogs, i.e. compounds in which the ring A exocyclic methylene group (carbon 19) typical of all vitamin D system has been removed and replaced by two hydrogen atoms. Structurally these novel analogs are characterized by the general formula I shown below:

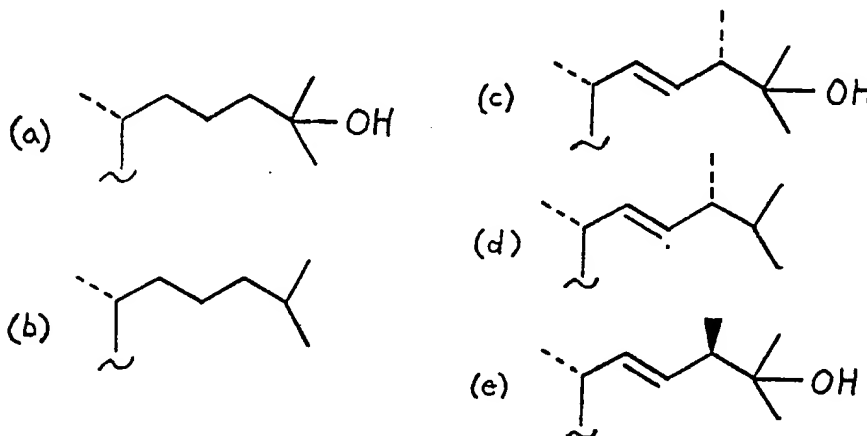


where X¹ and X² are each selected from the group consisting of hydrogen and acyl, and where the group R represents any of the typical side chains known for vitamin D type compounds. Thus, R may be an alkyl, hydrogen, hydroxyalkyl or fluoroalkyl group, or R may represent the following side chain:



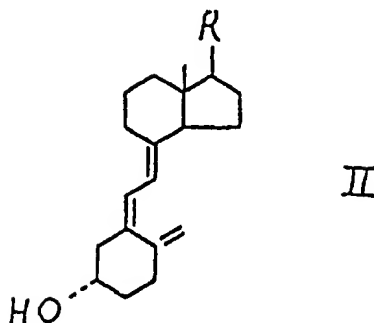
wherein R^1 represents hydrogen, hydroxy or O-acyl, R^2 and R^3 are each selected from the group consisting of alkyl, hydroxyalkyl and fluoroalkyl, or, when taken together represent the group $-(CH_2)_m-$ where m is an integer having a value of from 2 to 5, R^4 is selected from the group consisting of hydrogen, hydroxy, fluorine, O-acyl, alkyl, hydroxyalkyl and fluoroalkyl, R^5 is selected from the group consisting of hydrogen, fluorine, alkyl, hydroxyalkyl and fluoroalkyl, or, R^4 and R^5 taken together represent double-bonded oxygen, R^6 and R^7 are each selected from the group consisting of hydrogen, hydroxy, O-acyl, fluorine and alkyl, or, R^6 and R^7 taken together form a carbon-carbon double bond, and wherein n is an integer having a value of from 1 to 5, and wherein the carbon at any one of positions 20, 22, or 23 in the side chain may be replaced by an O, S, or N atom.

Specific important examples of side chains are the structures represented by formulas (a), (b), (c), (d) and (e) below, i.e. the side chain as it occurs in 25-hydroxyvitamin D_3 (a); vitamin D_3 (b); 25-hydroxyvitamin D_2 (c); vitamin D_2 (d); and the C-24-epimer of 25-hydroxyvitamin D_2 (e).



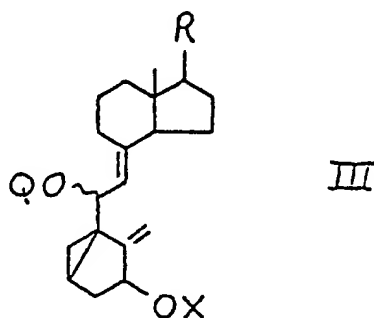
In this specification and the claims, the term 'alkyl' signifies an alkyl radical of 1 to 5 carbons in all isomeric forms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, etc., and the terms 'hydroxyalkyl' and 'fluoroalkyl' refer to such an alkyl radical substituted by one or more hydroxy or fluoro groups respectively, and the term 'acyl' means an aliphatic acyl group of 1 to 5 carbons, such as formyl, acetyl, propionyl, etc. or an aromatic acyl group such as benzoyl, nitrobenzoyl or halobenzoyl. The term 'aryl' signifies a phenyl-, or an alkyl-, nitro- or halo-substituted phenyl group.

The preparation of 1 α -hydroxy-19-nor-vitamin D compounds having the basic structure shown above can be accomplished by a common general method, using known vitamin D compounds as starting materials. Suitable starting materials are, for example, the vitamin D compounds of the general structure II:



where R is any of the side chains as defined above. These vitamin D starting materials are known compounds, or compounds that can be prepared by known methods.

Using the procedure of DeLuca et al. (U.S. Patent 4,195,027), the starting material can be converted to the corresponding 1 α -hydroxy-3,5-cyclovitamin D derivative, having the general structure III below, where X represents hydrogen and Q represents an alkyl, preferably methyl:

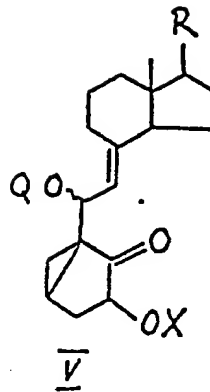
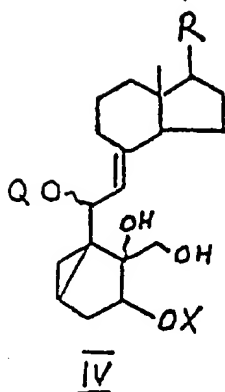


So as to preclude undesired reaction of the 1 α -hydroxy group in subsequent steps, the hydroxy group is converted to the corresponding acyl derivative, i.e. the compound III shown above, where X represents an acyl group, using standard acylation procedures, such as treatment with an acyl anhydride or acyl halide in pyridine at room temperature or slightly elevated temperature (30-70°C). It should be understood also that whereas the process of this invention is illustrated here with acyl protection of hydroxy functions, alternative standard hydroxy-protecting groups can also be used, such as, for example, alkylsilyl or alkoxyalkyl groups. Such protecting groups are well-known in the art (e.g. trimethylsilyl, triethylsilyl, t.-butyldimethylsilyl, or tetrahydrofuranyl, methoxymethyl), and their use is considered a routine modification of experimental detail within the scope of the process of this invention.

The derivative as obtained above can then be reacted with, say osmium tetroxide, to produce the 10,18-dihydroxy analog, IV (where X is acyl), which is subjected to diol cleavage using sodium metaperiodate or similar vicinal diol cleavage reagents (e.g. lead tetraacetate) to obtain the 10-oxo-intermediate, having the structure V below (where X is acyl):

5

10



15

These two consecutive steps can be carried out according to the procedures given by Paaren et al. [J. Org. Chem. 48, 3819 (1983)]. If the side chain unit, R, carries vicinal diols (e.g. 24,25-dihydroxy or 25,26-dihydroxy, etc.), these, of course, also need to be protected, e.g. via acylation, silylation, or as the isopropylidene derivative prior to the periodate cleavage reactions.

20

In most cases, the acylation of the 1 α -hydroxy group as mentioned above will simultaneously effect the acylation of side chain hydroxy functions, and these acylation conditions can, of course, be appropriately adjusted (e.g. elevated temperatures, longer reaction times) so as to assure complete protection of side chain vicinal diol groupings

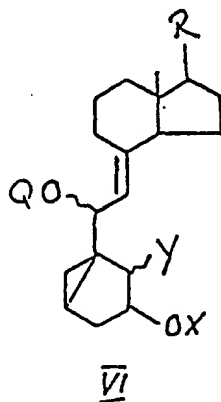
25

The next step of the process comprises the reduction of the 10-oxo-group to the corresponding 10-alcohol having the structure VI shown below (where X is acyl and Y represents hydroxy). When X is acyl, this reduction is carried out conveniently in an organic solvent at from, say, 0°C to room temperature, using NaBH₄ or equivalent hydride reducing agents, selective for the reduction of carbonyl groups without cleaving ester functions. Obviously, when X is a hydroxy-protecting group that is stable to reducing agents, any of the other hydride reducing agents (e.g. LiAlH₄, or analogous reagents) may be employed also.

30

35

40



45

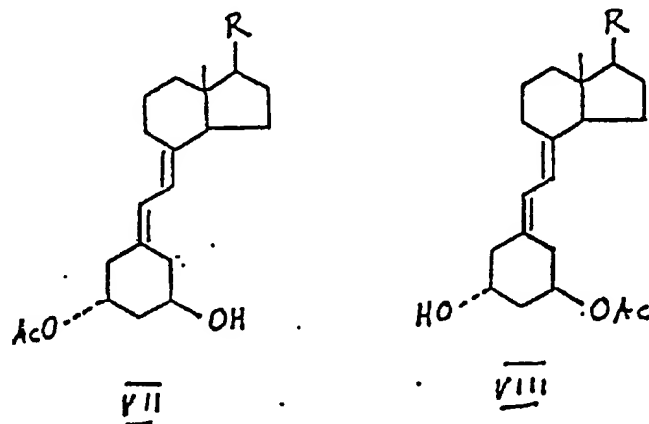
The 10-hydroxy intermediate can then be treated with an alkyl- or arylsulfonylhalide (e.g. methanesulfonylchloride) in a suitable solvent (e.g. pyridine) to obtain the corresponding 10-O-alkyl- or arylsulfonyl derivative (the compound having the structure shown VI above, where Y is alkyl-SO₂O-, or aryl-SO₂O-, and this sulfonate intermediate is then directly reduced, e.g. with lithium aluminum hydride, or the analogous known lithium aluminum alkyl hydride reagents in an ether solvent, at a temperature typically from 0°C to the boiling temperature of the solvent, thereby displacing the sulfonate group and obtaining the 10-deoxy derivative, represented by the structure VI above, where X and Y are both hydrogen. As shown by the above structure, a 1-O-acyl function in the precursor compound V is also cleaved in this reduction step to produce the free 1 α -hydroxy function, and any O-acyl protecting group in the side chain would, of course, likewise be reduced to the corresponding free alcohol function, as is well understood in the art. If desired, the hydroxy groups at C-1 (or hydroxy groups in the side chain) can be reprotected by acylation or

50

55

silylation or ether formation to the corresponding acyl, alkylsilyl or alkoxyalkyl derivative, but such protection is not required. Alternative hydroxy-protecting groups, such as alkylsilyl or alkoxyalkyl groups would be retained in this reduction step, but can be removed, as desired, at this or later stages in the process by standard methods known in the art.

The above 1 α -hydroxy-10-deoxy cyclovitamin D intermediate is next solvolysed e.g. the presence of a low-molecular weight organic acid, using the conditions of DeLuca et al. (U.S. Patents 4,195,027 and 4,260,549). When the solvolysis is carried out in acetic acid, for example, there is obtained a mixture of 1 α -hydroxy-19-nor-vitamin D 3-acetate and 1 α -hydroxy-19-nor-vitamin D 1-acetate (compounds VII and VIII, below), and the analogous 1- and 3-acylates are produced, when, alternative acids are used for solvolysis.



Direct basic hydrolysis of this mixture under standard conditions then produces the desired 1 α -hydroxy-19-nor-vitamin D compounds of structure I above (where X¹ and X² are hydrogen). Alternatively, the above mixture of monoacetates or other acylates may also be separated (e.g. by high pressure liquid chromatography) and the resulting 1-acetate and 3-acetate isomers may be subjected separately to hydrolysis to obtain the same final product from each, namely the 1 α -hydroxy-19-nor-vitamin D compounds of structure I. Also the separated monoacetates of structure VII or VIII or the free 1,3-dihydroxy compound can of course, be reacylated according to standard procedures with any desired acyl group, so as to produce the product of structure I above, where X¹ and X² represent acyl groups which may be the same or different.

Biological Activity of 1 α -Hydroxy-19-Nor-Vitamin D Compounds

The novel compounds of this invention exhibit an unexpected pattern of biological activity, namely high potency in promoting the differentiation of malignant cells and little or no activity in calcifying bone tissue. This is illustrated by the biological assay results obtained for 1 α ,25-dihydroxy-19-nor-vitamin D₃ (compounds Ia), which are summarized in Tables 1 and 2, respectively. Table 1 shows a comparison of the activity of the known active metabolite 1 α ,25-dihydroxyvitamin D₃ and the 19-nor analog (Ia) in inducing the differentiation of human leukemia cells (HL-60 cells) in culture to normal cells (monocytes). Differentiation activity was assessed by three standard differentiation assays, abbreviated in Table 1 as NBT (nitroblue tetrazolium reduction), NSE (non-specific esterase activity), and PHAGO (phagocytosis activity). The assays were conducted according to known procedures, as given, for example, by DeLuca et al. (U.S. Patent 4,717,721) and Ostrem et al., J. Biol. Chem. 262, 14164, 1987). For each assay, the differentiation activity of the test compounds is expressed in terms of the percent of HL-60 cells having differentiated to normal cells in response to a given concentration of test compound.

The results summarized in Table 1 clearly show that the new analog, 1 α ,25-dihydroxy-19-nor-vitamin D₃ (Ia) is as potent as 1 α ,25-dihydroxyvitamin D₃ in promoting the differentiation of leukemia cells. Thus in all three assays close to 90% of the cells are induced to differentiate by 1 α ,25-dihydroxyvitamin D₃ at a concentration of 1×10^{-7} molar, and the same degree of differentiation (i.e. 90, 84 and 90%) is achieved by the 19-nor analog (Ia).

Table 1

Differentiation of HL-60 Cells			
1 α ,25-dihydroxyvitamin D ₃	% Differentiated Cells		
(moles/liter)	(mean \pm SEM)		
	NBT	NSE	PHAGO
1 \times 10 ⁻⁷	86 \pm 2	89 \pm 1	87 \pm 3
1 \times 10 ⁻⁸	60 \pm 2	60 \pm 3	64 \pm 2
1 \times 10 ⁻⁹	33 \pm 2	31 \pm 2	34 \pm 1
1 α ,25-dihydroxy-19-nor-vitamin D ₃ , (Ia)			
(moles/liter)			
2 \times 10 ⁻⁷	94 \pm 2	95 \pm 3	94 \pm 2
1 \times 10 ⁻⁷	90 \pm 4	84 \pm 4	90 \pm 4
5 \times 10 ⁻⁸	72 \pm 3	73 \pm 3	74 \pm 3
1 \times 10 ⁻⁸	61 \pm 3	60 \pm 3	56 \pm 1
1 \times 10 ⁻⁹	32 \pm 1	31 \pm 1	33 \pm 1

In contrast to the preceding results, the new 19-nor analog (Ia) exhibits no activity in an assay measuring the calcification of bone, a typical response elicited by vitamin D compounds. Relevant data, representing the results of an assay comparing the bone calcification activity in rats of 1 α ,25-dihydroxyvitamin D₃ and 1 α ,25-dihydroxy-19-nor-vitamin D₃ (Ia), are summarized in Table 2. This assay was conducted according to the procedure described by Tanaka et al., Endocrinology 92, 417 (1973).

The results presented in Table 2 show the expected bone calcification activity of 1 α ,25-dihydroxyvitamin D₃ as reflected by the increase in percent bone ash, and in total ash at all dose levels. In contrast, the 19-nor analog Ia exhibits no activity at all three dose levels, when compared to the vitamin D-deficient (-D) control group.

Table 2

Calcification Activity			
Compound	Amount Administered*	% Ash	Total Ash (mg)
	(pmoles/day/7 days)	(mean \pm SEM)	(mean \pm SEM)
-D (control)	0	19 \pm 0.8	23 \pm 1.2
1 α ,25-dihydroxy-vitamin D ₃	32.5	23 \pm 0.5	34 \pm 1.6
	65.0	26 \pm 0.7	36 \pm 1.1
	325.0	28 \pm 0.9	40 \pm 1.9
1 α ,25-dihydroxy-19-nor-vitamin D ₃ (Ia)	32.5	22 \pm 0.9	28 \pm 1.6
	65.0	19 \pm 1.5	28 \pm 3.4
	325.0	19 \pm 1.2	30 \pm 2.4

* Each assay group comprised 6 rats, receiving the indicated amount of test compound by intraperitoneal injection daily for a period of seven days.

Thus the new 19-nor analog shows a selective activity profile combining high potency in inducing the differentiation of malignant cells with very low or no bone calcification activity. The compounds of this novel structural class, therefore, can be useful as therapeutic agents for the treatment of malignancies. Because the differentiative activity of vitamin D compounds on keratinocytes of skin (Smith et al., J. Invest. Dermatol.

86, 709, 1986; Smith et al., J. Am. Acad. Dermatol. 19, 516, 1988) is believed to be an indication of successful treatment of psoriasis (Takamoto et al., Calc. Tissue Int. 39, 360, 1986), these compounds should prove useful in treating this and other skin disorders characterized by proliferation of undifferentiated skin cells. These compounds should also find use in the suppression of parathyroid tissue, as for example, in cases of secondary hyperparathyroidism found in renal disease (Slatopolsky et al., J. Clin. Invest. 74, 2136, 1984).

For treatment purposes, the novel compounds of this invention can be formulated, for example, as solutions in innocuous solvents or as emulsions, suspensions or dispersions in suitable innocuous solvents or carriers, or as pills, tablets or capsules, containing solid carriers according to conventional methods known in the art. For topical applications the compounds are advantageously formulated as creams or ointments or similar vehicle suitable for topical applications. Any such formulations may also contain other pharmaceutically-acceptable and non-toxic excipients such as stabilizers, anti-oxidants, binders, coloring agents or emulsifying or taste-modifying agents.

The compounds are advantageously administered by injection, or by intravenous infusion of suitable sterile solutions, or in the form of oral doses via the alimentary canal, or topically in the form of ointments, lotions, or in suitable transdermal patches. For the treatment of malignant diseases, the 19-nor-vitamin D compounds of this invention should be administered to subjects in dosages sufficient to inhibit the proliferation of malignant cells and induce their differentiation into normal monocyte-macrophages. Similarly, for the treatment of psoriasis, the compounds may be administered orally or topically in amounts sufficient to arrest the proliferation of undifferentiated keratinocytes, and in the treatment of hyperparathyroidism, the compounds should be administered in dosages sufficient to suppress parathyroid activity, so as to achieve parathyroid hormone levels in the normal range. Suitable dosage amounts are from 1 to 500 µg of compound per day, such dosages being adjusted, depending on diseases to be treated, its severity and the response or condition of the subject as well-understood in the art.

This invention is more specifically described by the following illustrative examples. In these examples specific products identified by Roman numerals and letters, i.e. Ia, Ib, ..., IIa, IIb, ..., etc. refer to the specific structures and side chain combinations identified in the preceding description.

Example 1

Preparation of 1α,25-dihydroxy-19-nor-vitamin D₃ (Ia)

(a) 1α,25-Dihydroxy-3,5-cyclovitamin D₃ 1-acetate, 6-methyl ether:

Using 25-hydroxyvitamin D₃ (IIa) as starting material, the known 1α,25-dihydroxy-3,5-cyclovitamin D₃ derivative IIIa (X=H) was prepared according to published procedures (DeLuca et al., U.S. Patent 4, 195,027 and Paaren et al., J. Org. Chem. 45, 3252 (1980)). This product was then acetylated under standard conditions to obtain the corresponding 1-acetate derivative IIIa (X=Ac).

(b) 10,19-Dihydro-1α,10,19,25-tetrahydroxy-3,5-cyclovitamin D₃ 1-acetate, 6-methyl ether (IVa):

Intermediate IIIa (X=Ac) was treated with a slight molar excess of osmium tetroxide in pyridine according to the general procedure described by Paaren et al. (J. Org. Chem. 48, 3819 (1983)) to obtain the 10,19-dihydroxylated derivative IVa. Mass spectrum m/z (relative intensity), 508 (M⁺, 1), 488 (2), 474 (40), 425 (45), 396 (15), 285 (5), 229 (30), 133 (45), 59 (80), 43 (100). ¹H NMR (CDCl₃) δ 0.52 (3H, s, 18-CH₃), 0.58 (1H, m, 3-H), 0.93 (3H, d, J=6.1 Hz, 21-CH₃), 1.22 (6H, s, 26-CH₃ and 27-CH₃), 2.10 (3H, s, COCH₃), 3.25 (3H, s, 6-OCH₃), 3.63 (2H, m, 19-CH₂), 4.60 (1H, d, J=9.2 Hz, 6-H), 4.63 (1H, dd, 1β-H), 4.78 (1H, d, J=9.2 Hz, 7-H).

(c) 1α,25-Dihydroxy-10-oxo-3,5-cyclo-19-nor-vitamin D₃ 1-acetate, 6-methyl ether (Va):

The 10,19-dihydroxylated intermediate IVa was treated with a solution of sodium metaperiodate according to the procedure given by Paaren et al. (J. Org. Chem. 48, 3819, 1983) to produce the 10-oxo-

cyclovitamin D derivative (Va, X=Ac). Mass spectrum m/z (relative intensity) 442 (M^+ -MeOH) (18), 424 (8), 382 (15), 364 (35), 253 (55), 225 (25), 197 (53), 155 (85), 137 (100). ^1H NMR (CDCl_3) δ 0.58 (3H, s, 18- CH_3), 0.93 (3H, d, $J=6.6$ Hz, 21- CH_3), 1.22 (6H, s, 26- CH_3 and 27- CH_3), 2.15 (s, 3- OCOCH_3), 3.30 (3H, s, 6- OCH_3), 4.61 (1H, d, $J=9.1$ Hz, 6-H), 4.71 (1H, d, $J=9.6$ Hz, 7-H), 5.18 (1H, m, 1 β -H).

5 It has been found also that this diol cleavage reaction does not require elevated temperatures, and it is, indeed, generally preferable to conduct the reaction at approximately room temperature.

(d) 1 α -Acetoxy-10,25-dihydroxy-3,5-cyclo-19-nor-vitamin D₃ 6-methyl ether (Via, X=Ac, Y=OH):

10 The 10-oxo derivative Va (X=Ac) (2.2 mg, 4.6 μmol) was dissolved in 0.5 ml of ethanol and to this solution 50 μl (5.3 μmol) of a NaBH_4 solution (prepared from 20 mg of NaBH_4 , 4.5 ml water and 0.5 ml of 0.01 N NaOH solution) was added and the mixture stirred at 0°C for ca. 1.5 h, and then kept at 0°C for 18 h. To the mixture ether was added and the organic phase washed with brine, dried over MgSO_4 , filtered and
15 evaporated. The crude product was purified by column chromatography on a 15 x 1 cm silica gel column and the alcohol Via (X=Ac, Y=OH) was eluted with ethyl acetate hexane mixtures to give 1.4 mg (3 μmol) of product. Mass spectrum m/z (relative intensity) 476 (M^+) (1), 444 (85), 426 (18), 384 (30), 366 (48), 351 (21), 255 (35), 237 (48), 199 (100), 139 (51), 59 (58).

20

(e) 1 α ,25-Dihydroxy-19-nor-vitamin D₃ (Ia, X'=X²=H):

The 10-alcohol (Via, X=Ac, Y=OH) (1.4 mg) was dissolved in 100 μl anhydrous CH_2Cl_2 and 10 μl (14 μmol) triethylamine solution [prepared from 12 mg (16 μl) triethylamine in 100 μl anhydrous CH_2Cl_2],
25 followed by 7 μl (5.6 μmol) mesyl chloride solution (9 mg mesyl chloride, 6.1 μl , in 100 μl anhydrous CH_2Cl_2) added at 0°C. The mixture was stirred at 0°C for 2 h. The solvents were removed with a stream of argon and the residue (comprising compound Via, X=Ac, Y= $\text{CH}_3\text{SO}_2\text{O}-$) dissolved in 0.5 ml of anhydrous tetrahydrofuran; 5 mg of LiAlH_4 was added at 0°C and the mixture kept at 0°C for 16h. Excess LiAlH_4 was decomposed with wet ether, the ether phase was washed with water and dried over MgSO_4 , filtered and
30 evaporated to give the 19-nor product Via (X=Y=H).

This product was dissolved in 0.5 ml of acetic acid and stirred at 55°C for 20 min. The mixture was cooled, ice water added and extracted with ether. The ether phase was washed with cold 10% sodium bicarbonate solution, brine, dried over MgSO_4 , filtered and evaporated to give the expected mixture of 3-acetoxy-1 α -hydroxy- and 1 α -acetoxy-3-hydroxy isomers, which were separated and purified by HPLC
35 (Zorbax Sil column, 6.4 x 25 cm, 2-propanol in hexane) to give about 70 μg each of compounds VIIa and XIll a. UV (in EtOH) λ_{max} 242.5 (OD 0.72), 251.5 (OD 0.86), 260 (OD 0.57).

Both 19-nor-1,25-dihydroxyvitamin D₃ acetates VIIa and VIIIa were hydrolyzed in the same manner. Each of the monoacetates was dissolved in 0.5 ml of ether and 0.5 ml 0.1 N KOH in methanol was added. The mixture was stirred under argon atmosphere for 2 h. More ether was added and the organic phase
40 washed with brine, dried over anhydrous MgSO_4 , filtered and evaporated. The residue was dissolved in a 1:1 mixture of 2-propanol and hexane and passed through a Sep Pak column and washed with the same solvent. The solvents were evaporated and the residue purified by HPLC (Zorbax Sil, 6.4 x 25 cm, 10% 2-propanol in hexane). The hydrolysis products of VIIa and VIIIa were identical and gave 66 μg of Ia (X'=X²=H). Mass spectrum (m/z relative intensity) 404 (M^+) (100), 386 (41), 371 (20), 275 (53), 245 (51),
45 180 (43), 135 (72), 133 (72), 95 (82), 59 (18), exact mass calcd. for $\text{C}_{26}\text{H}_{44}\text{O}_3$ 404.3290, found 404.3272. ^1H NMR (CDCl_3) δ 0.52 (3H, s, 18- CH_3), 0.92 (3H, d, $J=6.9$ Hz, 21- CH_3), 1.21 (6H, s, 26- CH_3 and 27- CH_3), 4.02 (1H, m, 3 α -H), 4.06 (1H, m, 1 β -H), 5.83 (1H, d, $J=11.6$ Hz, 7-H), 6.29 (1H, d, $J=10.7$ Hz, 6-H). UV (in EtOH), λ_{max} 243 (OD 0.725), 251.5 (OD 0.823), 261 (OD 0.598).

50

Example 2

Preparation of 1 α -hydroxy-19-nor-vitamin D₃ (Ib)

55

(a) With vitamin D₃ (IIb) as starting material, and utilizing the conditions of Example 1a, there is obtained known 1 α -hydroxy-3,5-cyclovitamin D₃ 1-acetate, 6-methyl ether, compound IIIb (X=Ac).

(b) By subjecting intermediate IIIb (X=Ac), as obtained in Example 2a above to the conditions of

Example 1b, there is obtained 10,19-dihydro-1 α ,10,19-trihydroxy-3,5-cyclovitamin D₃ 1-acetate, 6-methyl ether IVb (X=Ac).

(c) By treatment of intermediate IVb (X=Ac) with sodium metaperiodate according to Example 1c above, there is obtained 1 α -hydroxy-10-oxo-3,5-cyclo-19-nor-vitamin D₃ 1-acetate, 6-methyl ether Vb (X=Ac).

(d) Upon reduction of the 10-oxo-intermediate Vb (X=Ac) under the conditions of Example 1d above, there is obtained 1 α -acetoxy-10-hydroxy-3,5-cyclo-19-nor-vitamin D₃ 6-methyl ether VIb (X=Ac, Y=OH).

(e) Upon processing intermediate VIb (X=Ac, Y=OH) through the procedure given in Example 1e above, there is obtained 1 α -hydroxy-19-nor-vitamin D₃ (Ib, X¹=X²=H).

Example 3

Preparation of 1 α ,25-dihydroxy-19-nor-vitamin D₂

(a) Utilizing 25-hydroxyvitamin D₂ (IIc) as starting material and experimental conditions analogous to those of Example 1a, there is obtained 1 α ,25-dihydroxy-3,5-cyclovitamin D₂ 1-acetate, 6-methyl ether, compound IIIc (X=Ac).

(b) Subjecting intermediate IIIc (X=Ac), as obtained in Example 3a above, to the reaction conditions of Example 1b, provides 10,19-dihydro-1 α ,10,19,25-tetrahydroxy-3,5-cyclovitamin D₂ 1-acetate, 6-methyl ether, IVc (X=Ac).

(c) By treatment of intermediate IVc (X=Ac) with sodium metaperiodate according to general procedures of Example 1c above, there is obtained 1 α ,25-dihydroxy-10-oxo-3,5-cyclo-19-nor-vitamin D₂ 1-acetate, 6-methyl ether Vc (X=Ac).

(d) Upon reduction of the 10-oxo-intermediate Vc (X=Ac) under conditions analogous to those of Example 1d above, there is obtained 1 α -acetoxy-10,25-dihydroxy-3,5-cyclo-19-nor-vitamin D₂ 6-methyl ether VIc (X=Ac, Y=OH).

(e) Upon processing intermediate VIc (X=Ac, Y=OH) through the procedural steps given in Example 1e above, there is obtained 1 α ,25-dihydroxy-19-nor-vitamin D₂ (Ic, X¹-X²=H).

Example 4

Preparation of 1 α -hydroxy-19-nor-vitamin D₂

(a) With vitamin D₂ (IIc) as starting material, and utilizing the conditions of Example 1a, there is obtained known 1 α -hydroxy-3,5-cyclovitamin D₂ 1-acetate, 6-methyl ether, compound IIIc (X=Ac).

(b) By subjecting intermediate IIIc (X=Ac), as obtained in Example 4a above to the conditions of Example 1b, there is obtained 10,19-dihydro-1 α ,10,19-trihydroxy-3,5-cyclovitamin D₂ 1-acetate, 6-methyl ether, IVc (X=Ac).

(c) By treatment of intermediate IVc (X=Ac) with sodium metaperiodate according to Example 1c above, there is obtained 1 α -hydroxy-10-oxo-3,5-cyclo-19-nor-vitamin D₂ 1-acetate, 6-methyl ether, Vc (X=Ac).

(d) Upon reduction of the 10-oxo-intermediate Vc (X=Ac) under the conditions of Example 1d above, there is obtained 1 α -acetoxy-10-hydroxy-3,5-cyclo-19-nor-vitamin D₂ 6-methyl ether, VIc (X=Ac, Y=OH).

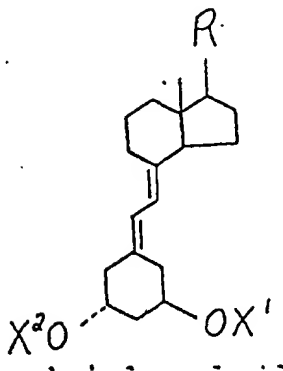
(e) Upon processing intermediate VIc (X=Ac, Y=OH) through the procedure given in Example 1e above, there is obtained 1 α -hydroxy-19-nor-vitamin D₂ (Id, X¹=X²=H).

Claims

1. A compound having the formula:

5

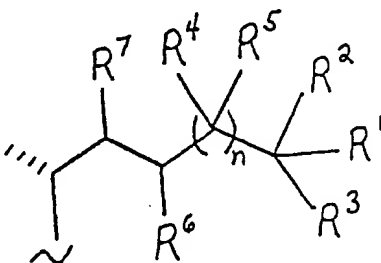
10



15 where X¹ and X² are each independently hydrogen, acyl, alkylsilyl or alkoxyalkyl, and R is alkyl, hydrogen, hydroxyalkyl, fluoroalkyl or a side chain of the formula:

20

25



wherein R¹ represents hydrogen, hydroxy or O-acyl, R² and R³ are each independently alkyl, hydroxyalkyl or fluoroalkyl, or, when taken together represent the group -- (CH₂)_m -- where m is an integer from 2 to 5, R⁴ is hydrogen, hydroxy, fluorine, O-acyl, alkyl, hydroxyalkyl or fluoroalkyl, R⁵ is hydrogen, fluorine, alkyl, hydroxyalkyl or fluoroalkyl, or R⁴ and R⁵ taken together represent double-bonded oxygen, R⁶ and R⁷ are each independently hydrogen, hydroxy, O-acyl, fluorine or alkyl, or, R⁶ and R⁷ taken together form a carbon-carbon double bond, and n is an integer from 1 to 5 and wherein the carbon at any one of positions 20, 22 or 23 in the side chain may be replaced by an O, S, or N atom.

35 2. A compound according to claim 1 wherein X¹ and X² are both hydrogen, R¹ is hydroxy, R² and R³ are each independently methyl, trifluoromethyl, ethyl or propyl, R⁶ and R⁷ are both hydrogen, or together form a carbon-carbon double bond, R⁴ and R⁵ are both hydrogen and n is 1, 2 or 3.

3. 1α,25-Dihydroxy-19-nor-vitamin D₃.

4. 1α-Hydroxy-19-nor-vitamin D₃.

40 5. 1α,25-Dihydroxy-19-nor-vitamin D₂.

6. 1α-Hydroxy-19-nor-vitamin D₂.

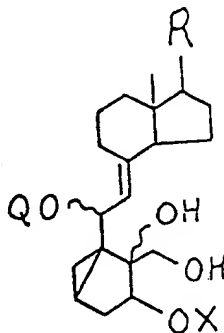
7. 1α-Hydroxy-19-nor-24 epi-vitamin D₂.

8. 1α,25-Dihydroxy-19-nor-24 epi-vitamin D₂.

45 9. A compound having the formula:

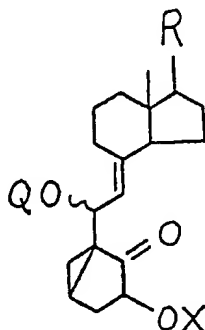
50

55



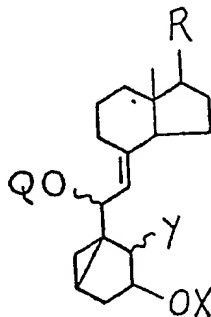
wherein R is as defined in Claim 1, Q represents alkyl and X is hydrogen, acyl, alkylsilyl or alkoxyalkyl.

10. A compound having the formula:



wherein R is as defined in Claim 1, Q represents alkyl and X is hydrogen, acyl, alkylsilyl or alkoxyalkyl.

11. A compound having the formula:



wherein R is as defined in Claim 1, Q represents alkyl, X is hydrogen, acyl, alkylsilyl or alkoxyalkyl, and Y is hydroxy, hydrogen or protected hydroxy where the protecting group is acyl, alkylsilyl or alkoxyalkyl.

12. A pharmaceutical composition which comprises at least one compound as claimed in any one of claims 1 to 8 together with a pharmaceutically acceptable excipient.

13. A composition according to claim 12 wherein the compound is in a solid or liquid vehicle ingestible by, and non-toxic to, mammals.

14. A composition according to claim 12 or 13 wherein the compound is 1 α ,25-hydroxy-19-nor-vitamin D₃, 1 α -hydroxy-19-nor-vitamin D₃, 1 α ,25-dihydroxy-19-nor-vitamin D₂ or 1 α -hydroxy-19-nor-vitamin D₂.

15. A composition according to any one of claims 12 to 14 which contains from 0.5 μ g to 50 μ g of the compound.

16. A composition according to any one of claims 12 to 15 which is suitable for topical administration.

17. A composition according to any one of claims 12 to 15 which is suitable for parenteral administration.

18. A composition according to any one of claims 12 to 15 which is suitable for oral administration.

19. A compound as defined in any one of claims 1 to 8 for inducing cell differentiation in malignant cells.

20. A compound as defined in any one of claims 1 to 8 for inducing cell differentiation in leukemia cells.

21. A compound as defined in any one of claims 1 to 8 for treating a proliferative skin disorder in a mammal.

22. A compound as defined in any one claims 1 to 8 for treating psoriasis.

23. A compound as defined in any one of claims 1 to 8 for treating primary or secondary hyperparathyroidism.

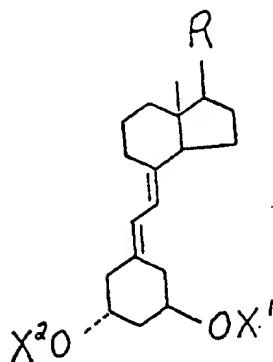
24. A compound as defined in any one of claims 1 to 8 for treating a neoplastic disease.

25. A compound as defined in any one of claims 1 to 8 for use in the treatment of a condition as defined in any one of claims 19 to 24

26. A process for preparing a compound having the formula:

5

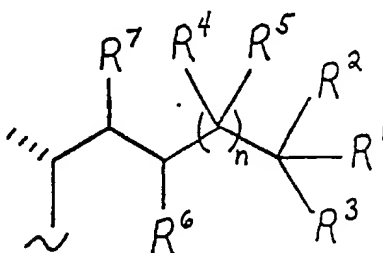
10



15 where X^1 and X^2 are each independently hydrogen, acyl, alkylsilyl or alkoxyalkyl, and R is alkyl, hydrogen, hydroxyalkyl, fluoroalkyl or a side chain of the formula:

20

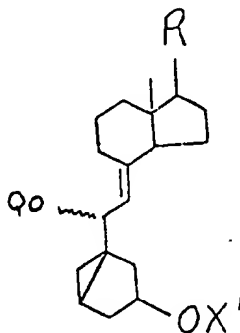
25



30 wherein R^1 represents hydrogen, hydroxy or O-acyl, R^2 and R^3 are each independently alkyl, hydroxyalkyl or fluoroalkyl, or, when taken together represent the group $-(CH_2)_m-$ where m is an integer from 2 to 5, R^4 is hydrogen, hydroxy, fluorine, O-acyl, alkyl, hydroxyalkyl or fluoroalkyl, R^5 is hydrogen, fluorine, alkyl, hydroxyalkyl or fluoroalkyl, or R^4 and R^5 taken together represent double-bonded oxygen, R^6 and R^7 are each independently hydrogen, hydroxy, O-acyl, fluorine or alkyl, or, R^6 and R^7 taken together form a carbon-carbon double bond, and n is an integer from 1 to 5 and wherein the carbon at any one of positions 20, 22 or 23 in the side chain may be replaced by an O, S, or N atom characterised by solvolysing the 1 α -hydroxy-10-deoxy cyclovitamin D compound having the formula:

40

45



50

wherein Q is alkyl.

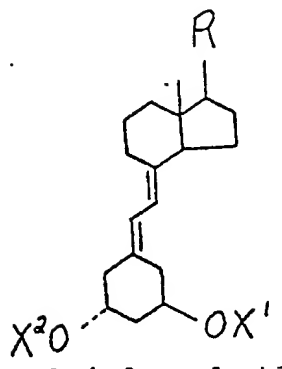
Amended claims in accordance with Rule 86(2) EPC.

55

1. A compound having the formula:

5

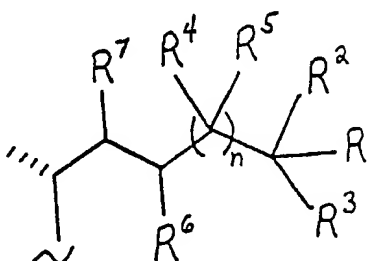
10



15 where X^1 and X^2 are each independently hydrogen, acyl, alkylsilyl or alkoxyalkyl, and R is alkyl, hydrogen, hydroxyalkyl, fluoroalkyl or a side chain of the formula:

20

25



30

35

wherein R^1 represents hydrogen, hydroxy or O-acyl, R^2 and R^3 are each independently alkyl, hydroxyalkyl or fluoroalkyl, or, when taken together represent the group $-(CH_2)_m-$ where m is an integer from 2 to 5, R^4 is hydrogen, hydroxy, fluorine, O-acyl, alkyl, hydroxyalkyl or fluoroalkyl, R^5 is hydrogen, fluorine, alkyl, hydroxyalkyl or fluoroalkyl, or R^4 and R^5 taken together represent double-bonded oxygen, R^6 and R^7 are each independently hydrogen, hydroxy, O-acyl, fluorine or alkyl, or, R^6 and R^7 taken together form a carbon-carbon double bond, and n is an integer from 1 to 5 and wherein the carbon at any one of positions 20, 22 or 23 in the side chain may be replaced by an O, S, or N atom.

2. A compound according to claim 1 wherein X^1 and X^2 are both hydrogen, R^1 is hydroxy, R^2 and R^3 are each independently methyl, trifluoromethyl, ethyl or propyl, R^6 and R^7 are both hydrogen, or together form a carbon-carbon double bond, R^4 and R^5 are both hydrogen and n is 1, 2 or 3.

3. $1\alpha,25$ -Dihydroxy-19-nor-vitamin D_3 .

4. 1α -Hydroxy-19-nor-vitamin D_3 .

40

5. $1\alpha,25$ -Dihydroxy-19-nor-vitamin D_2 .

6. 1α -Hydroxy-19-nor-vitamin D_2 .

7. 1α -Hydroxy-19-nor-24 epi-vitamin D_2 .

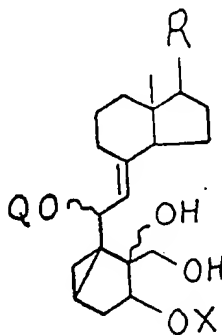
8. $1\alpha,25$ -Dihydroxy-19-nor-24 epi-vitamin D_2 .

45

9. A compound having the formula:

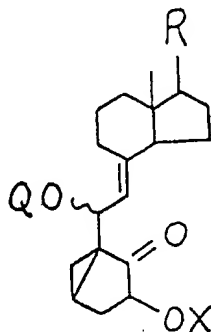
50

55



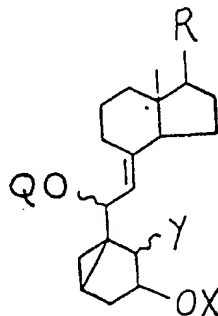
wherein R is as defined in Claim 1, Q represents alkyl and X is hydrogen, acyl, alkylsilyl or alkoxyalkyl.

10. A compound having the formula:



wherein R is as defined in Claim 1, Q represents alkyl and X is hydrogen, acyl, alkylsilyl or alkoxyalkyl.

11. A compound having the formula:



wherein R is as defined in Claim 1, Q represents alkyl, X is hydrogen, acyl, alkylsilyl or alkoxyalkyl, and Y is hydroxy, hydrogen or protected hydroxy where the protecting group is acyl, alkylsilyl or alkoxyalkyl.

12. A pharmaceutical composition which comprises at least one compound as claimed in any one of claims 1 to 8 together with a pharmaceutically acceptable excipient.

13. A composition according to claim 12 wherein the compound is in a solid or liquid vehicle ingestible by, and non-toxic to, mammals.

14. A composition according to claim 12 or 13 wherein the compound is 1 α ,25-hydroxy-19-nor-vitamin D₃, 1 α -hydroxy-19-nor-vitamin D₃, 1 α ,25-dihydroxy-19-nor-vitamin D₂ or 1 α -hydroxy-19-nor-vitamin D₂.

15. A composition according to any one of claims 12 to 14 which contains from 0.5 μ g to 50 μ g of the compound.

16. A composition according to any one of claims 12 to 15 which is suitable for topical administration.

17. A composition according to any one of claims 12 to 15 which is suitable for parenteral administration.

18. A composition according to any one of claims 12 to 15 which is suitable for oral administration.

19. A compound as defined in any one of claims 1 to 8 for inducing cell differentiation in malignant cells.

20. A compound as defined in any one of claims 1 to 8 for inducing cell differentiation in leukemia cells.

21. A compound as defined in any one of claims 1 to 8 for treating a proliferative skin disorder in a mammal.

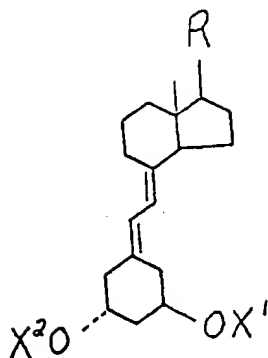
22. A compound as defined in any one claims 1 to 8 for treating psoriasis.

23. A compound as defined in any one of claims 1 to 8 for treating primary or secondary hyperparathyroidism.

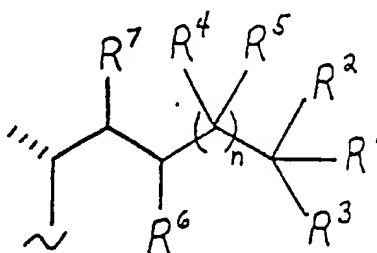
24. A compound as defined in any one of claims 1 to 8 for treating a neoplastic disease.

25. A compound as defined in any one of claims 1 to 8 for use in the treatment of a condition as defined in any one of claims 19 to 24

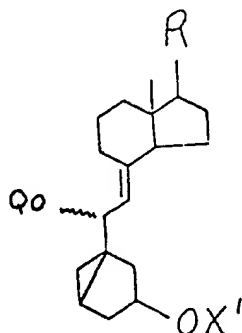
26. A process for preparing a compound having the formula:



20



35



45

50

55



Publication number: **0 387 077 B1**

EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification :
19.01.94 Bulletin 94/03

(51) Int. Cl.⁵: **C07C 401/00, A61K 31/59**

(21) Application number: **90302521.1**

(22) Date of filing: **09.03.90**

(54) 19-Nor vitamin D compounds.

(30) Priority: **09.03.89 US 321030**
16.02.90 US 481354

(43) Date of publication of application:
12.09.90 Bulletin 90/37

(45) Publication of the grant of the patent:
19.01.94 Bulletin 94/03

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IT LI LU NL SE

(56) References cited:
EP-A- 0 250 755
WO-A-85/03300
WO-A-86/02649
US-A- 4 448 726
JOURNAL OF THE CHEMICAL SOCIETY PER-
KIN TRANSACTIONS I, vol. 6, 1978, pages
590-595, London, GB; B. LYTHGOE et al.:
"Calciferol and its relatives. Part 22. A direct
total synthesis of vitamin D2 and vitamin
D3'2"

(73) Proprietor: **WISCONSIN ALUMNI RESEARCH**
FOUNDATION
614 North Walnut Street
Madison, WI 53705 (US)

(72) Inventor: **DeLuca, Hector F.**
1809 Highway BB Deerfield
Wisconsin 53531 (US)
Inventor: **Schnoes, Heinrich K.**
1806 Summit Avenue
Madison Wisconsin 53705 (US)
Inventor: **Perlman, Kato L.**
1 Chippewa Court
Madison Wisconsin 53711 (US)
Inventor: **Sicinski, Rafal R.**
University of Warsaw Dept. of Chemistry
02-093 Warsaw Pasteura 1 (PL)
Inventor: **Prahl, Jean Martin**
7 Georgetown Court
Madison Wisconsin 53919 (US)

(74) Representative: **Ellis-Jones, Patrick George**
Armine et al
J.A. KEMP & CO. 14 South Square Gray's Inn
London WC1R 5LX (GB)

Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent grant d. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid (Art. 99(1) European patent convention).

Description

This invention was made with United States government support awarded by the Department of Health and Human Services (NIH), Grant number: DK-14881. The United States Government has certain rights in this invention.

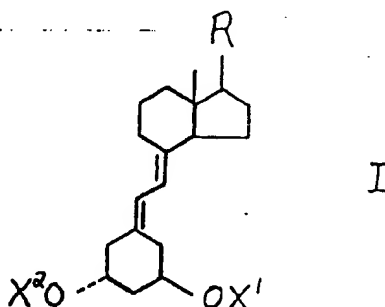
This invention relates to biologically active vitamin D compounds. More specifically, the invention relates to 19-nor-analogs of 1 α -hydroxylated vitamin D compounds and to a general process for their preparation.

Background

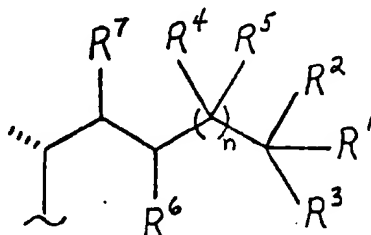
The 1 α -hydroxylated metabolites of vitamin D – most importantly 1 α ,25-dihydroxyvitamin D₃ (See US-A-3697559) and 1 α ,25-dihydroxyvitamin D₂ – are known as highly potent regulators of calcium homeostasis in animals and humans, and more recently their activity in cellular differentiation has also been established. As a consequence, many structural analogs of these metabolites, such as compounds with different side chain structures, different hydroxylation patterns, or different stereochemistry, have been prepared and tested. Important examples of such analogs are 1 α -hydroxyvitamin D₃, 1 α -hydroxyvitamin D₂, various side chain fluorinated derivatives of 1 α ,25-dihydroxyvitamin D₃, and side chain homologated analogs. Several of these known compounds exhibit highly potent activity *in vivo* or *in vitro*, and possess advantageous activity profiles and thus are in use, or have been proposed for use, in the treatment of a variety of diseases such as renal osteocytrophy, vitamin D-resistant rickets, osteoporosis, psoriasis, and certain malignancies.

Disclosure and Description of the Invention

A class of 1 α -hydroxylated vitamin D compounds not known heretofore are the 19-nor-analogs, i.e. compounds in which the ring A exocyclic methylene group (carbon 19) typical of all vitamin D system has been removed and replaced by two hydrogen atoms. Structurally these novel analogs are characterized by the general formula I shown below:



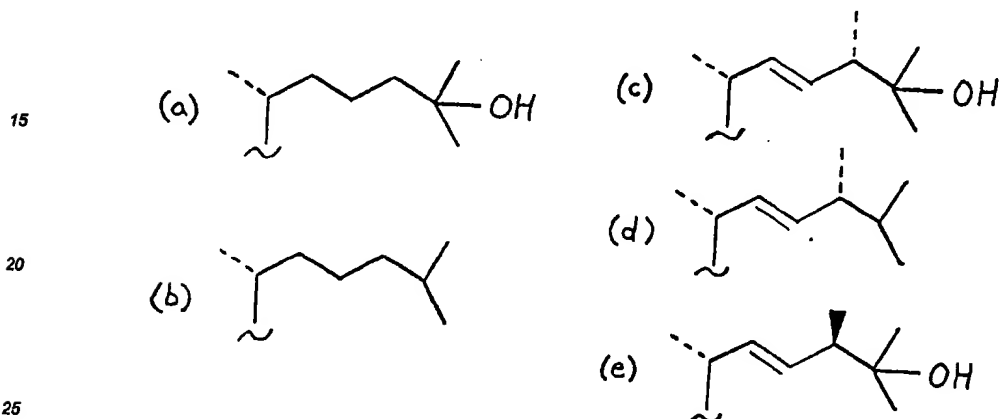
where X¹ and X² are each selected from the group consisting of hydrogen and acyl, and where the group R represents any of the typical side chains known for vitamin D type compounds. Thus, R may be an alkyl, hydrogen, hydroxyalkyl or fluoroalkyl group, or R may represent the following side chain:



wherein R¹ represents hydrogen, hydroxy or O-acyl, R² and R³ are each selected from the group consisting of alkyl, hydroxyalkyl and fluoroalkyl, or, when taken together represent the group -- (CH₂)_m -- where m is an integer having a value of from 2 to 5, R⁴ is selected from the group consisting of hydrogen, hydroxy, fluorine, O-

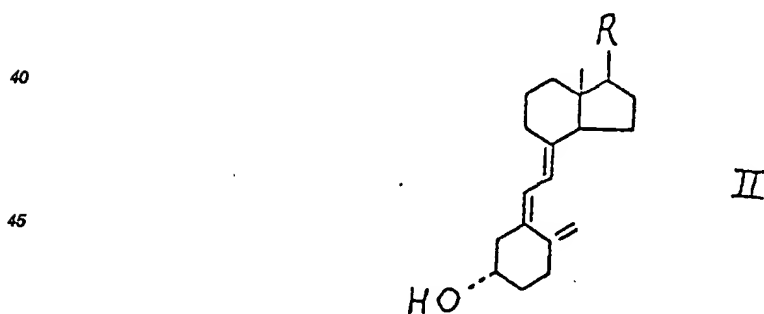
acyl, alkyl, hydroxyalkyl and fluoroalkyl, R^5 is selected from the group consisting of hydrogen, fluorine, alkyl, hydroxyalkyl and fluoroalkyl, or, R^4 and R^5 taken together represent double-bonded oxygen, R^6 and R^7 are each selected from the group consisting of hydrogen, hydroxy, O-acyl, fluorine and alkyl, or, R^6 and R^7 taken together form a carbon-carbon double bond, and wherein n is an integer having a value of from 1 to 5, and wherein the carbon at any one of positions 20, 22, or 23 in the side chain may be replaced by an O, S, or N atom.

Specific important examples of side chains are the structures represented by formulas (a), (b), (c), (d) and (e) below, i.e. the side chain as it occurs in 25-hydroxyvitamin D_3 (a); vitamin D_3 (b); 25-hydroxyvitamin D_2 (c); vitamin D_2 (d); and the C-24-epimer of 25-hydroxyvitamin D_2 (e).



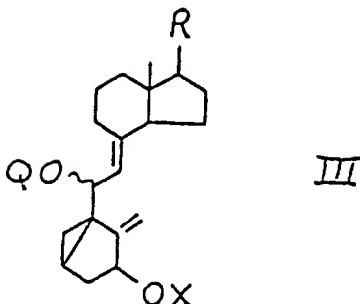
In this specification and the claims, the term 'alkyl' signifies an alkyl radical of 1 to 5 carbons in all isomeric forms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, etc., and the terms 'hydroxyalkyl' and 'fluoroalkyl' refer to such an alkyl radical substituted by one or more hydroxy or fluoro groups respectively, and the term 'acyl' means an aliphatic acyl group of 1 to 5 carbons, such as formyl, acetyl, propionyl, etc. or an aromatic acyl group such as benzoyl, nitrobenzoyl or halobenzoyl. The term 'aryl' signifies a phenyl-, or an alkyl-, nitro- or halo-substituted phenyl group.

The preparation of 1α -hydroxy-19-nor-vitamin D compounds having the basic structure shown above can be accomplished by a common general method, using known vitamin D compounds as starting materials. Suitable starting materials are, for example, the vitamin D compounds of the general structure II:



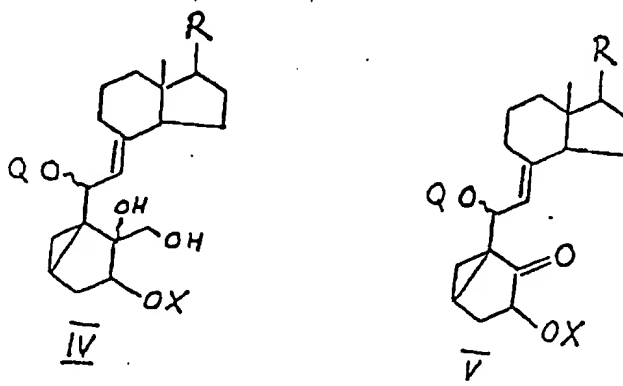
where R is any of the side chains as defined above. These vitamin D starting materials are known compounds, or compounds that can be prepared by known methods.

Using the procedure of DeLuca *et al.* (U.S. Patent 4,195,027), the starting material can be converted to the corresponding 1α -hydroxy-3,5-cyclovitamin D derivative, having the general structure III below, where X represents hydrogen and Q represents an alkyl, preferably methyl:



So as to preclude undesired reaction of the 1α -hydroxy group in subsequent steps, the hydroxy group is converted to the corresponding acyl derivative, i.e. the compound III shown above, where X represents an acyl group, using standard acylation procedures, such as treatment with an acyl anhydride or acyl halide in pyridine at room temperature or slightly elevated temperature (30-70°C). It should be understood also that whereas the process of this invention is illustrated here with acyl protection of hydroxy functions, alternative standard hydroxy-protecting groups can also be used, such as, for example, alkylsilyl or alkoxyalkyl groups. Such protecting groups are well-known in the art (e.g. trimethylsilyl, triethylsilyl, t-butyldimethylsilyl, or tetrahydrofuranyl, methoxymethyl), and their use is considered a routine modification of experimental detail within the scope of the process of this invention.

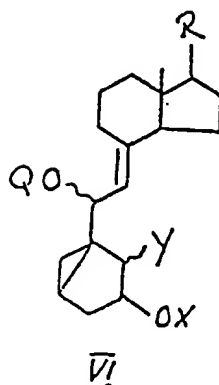
The derivative as obtained above can then be reacted with, say osmium tetroxide, to produce the 10,19-dihydroxy analog, IV (where X is acyl), which is subjected to diol cleavage using sodium metaperiodate or similar vicinal diol cleavage reagents (e.g. lead tetraacetate) to obtain the 10-oxo-intermediate, having the structure V below (where X is acyl):



These two consecutive steps can be carried out according to the procedures given by Paaren *et al.* [J. Org. Chem. 48, 3819 (1983)]. If the side chain unit, R, carries vicinal diols (e.g. 24,25-dihydroxy- or 25,26-dihydroxy, etc.), these, of course, also need to be protected, e.g. via acylation, silylation, or as the isopropylidene derivative prior to the periodate cleavage reactions.

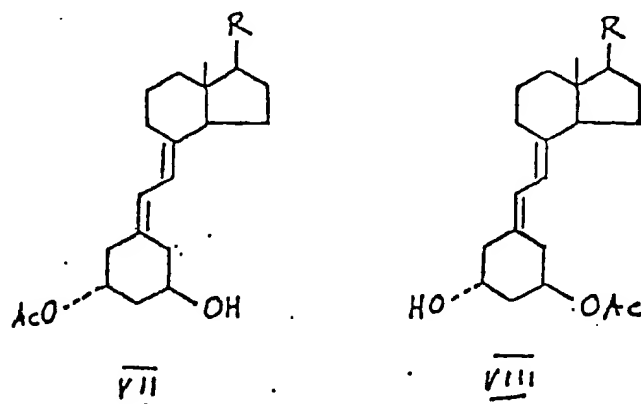
In most cases, the acylation of the 1α -hydroxy group as mentioned above will simultaneously effect the acylation of side chain hydroxy functions, and these acylation conditions can, of course, be appropriately adjusted (e.g. elevated temperatures, longer reaction times) so as to assure complete protection of side chain vicinal diol groupings.

The next step of the process comprises the reduction of the 10-oxo-group to the corresponding 10-alcohol having the structure VI shown below (where X is acyl and Y represents hydroxy). When X is acyl, this reduction is carried out conveniently in an organic solvent at from, say, 0°C to room temperature, using NaBH_4 or equivalent hydride reducing agents, selective for the reduction of carbonyl groups without cleaving ester functions. Obviously, when X is a hydroxy-protecting group that is stable to reducing agents, any of the other hydride reducing agents (e.g. LiAlH_4 , or analogous reagents) may be employed also.



The 10-hydroxy intermediate can then be treated with an alkyl- or arylsulfonylhalide (e.g. methanesulfonylchloride) in a suitable solvent (e.g. pyridine) to obtain the corresponding 10-O-alkyl- or arylsulfonyl derivative (the compound having the structure shown VI above, where Y is alkyl-SO₂O-, or aryl-SO₂O-, and this sulfonate intermediate is then directly reduced, e.g. with lithium aluminum hydride, or the analogous known lithium aluminum alkyl hydride reagents in an ether solvent, at a temperature typically from 0°C to the boiling temperature of the solvent, thereby displacing the sulfonate group and obtaining the 10-deoxy derivative, represented by the structure VI above, where X and Y are both hydrogen. As shown by the above structure, a 1-O-acyl function in the precursor compound V is also cleaved in this reduction step to produce the free 1α-hydroxy function, and any O-acyl protecting group in the side chain would, of course, likewise be reduced to the corresponding free alcohol function, as is well understood in the art. If desired, the hydroxy groups at C-1 (or hydroxy groups in the side chain) can be reprotected by acylation or silylation or ether formation to the corresponding acyl, alkylsilyl or alkoxyalkyl derivative, but such protection is not required. Alternative hydroxy-protecting groups, such as alkylsilyl or alkoxyalkyl groups would be retained in this reduction step, but can be removed, as desired, at this or later stages in the process by standard methods known in the art.

The above 1α-hydroxy-10-deoxy cyclovitamin D intermediate is next solvolysed e.g. the presence of a low-molecular weight organic acid, using the conditions of DeLuca *et al.* (U.S. Patents 4,195,027 and 4,260,549). When the solvolysis is carried out in acetic acid, for example, there is obtained a mixture of 1α-hydroxy-19-nor-vitamin D 3-acetate and 1α-hydroxy-19-nor-vitamin D 1-acetate (compounds VII and VIII, below), and the analogous 1- and 3-acylates are produced, when, alternative acids are used for solvolysis.



Direct basic hydrolysis of this mixture under standard conditions then produces the desired 1α-hydroxy-19-nor-vitamin D compounds of structure I above (where X¹ and X² are hydrogen). Alternatively, the above mixture of monoacetates or other acylates may also be separated (e.g. by high pressure liquid chromatography) and the resulting 1-acetate and 3-acetate isomers may be subjected separately to hydrolysis to obtain the same

final product from each, namely the 1 α -hydroxy-19-nor-vitamin D compounds of structure I. Also the separated monoacetates of structure VII or VIII or the 1,3-dihydroxy compound can, of course, be reacylated according to standard procedures with any desired acyl group, so as to produce the product of structure I above, where X¹ and X² represent acyl groups which may be the same or different.

Biological Activity of 1 α -Hydroxy-19-Nor-Vitamin D Compounds

The novel compounds of this invention exhibit an unexpected pattern of biological activity, namely high potency in promoting the differentiation of malignant cells and little or no activity in calcifying bone tissue. This is illustrated by the biological assay results obtained for 1 α ,25-dihydroxy-19-nor-vitamin D₃ (compounds Ia), which are summarized in Tables 1 and 2, respectively. Table 1 shows a comparison of the activity of the known active metabolite 1 α ,25-dihydroxyvitamin D₃ and the 19-nor analog (Ia) in inducing the differentiation of human leukemia cells (HL-60 cells) in culture to normal cells (monocytes). Differentiation activity was assessed by three standard differentiation assays, abbreviated in Table 1 as NBT (nitroblue tetrazolium reduction), NSE (non-specific esterase activity), and PHAGO (phagocytosis activity). The assays were conducted according to known procedures, as given, for example, by DeLuca *et al.* (U.S. Patent 4,717,721) and Ostrem *et al.*, J. Biol. Chem. 262, 14164, 1987). For each assay, the differentiation activity of the test compounds is expressed in terms of the percent of HL-60 cells having differentiated to normal cells in response to a given concentration of test compound.

The results summarized in Table 1 clearly show that the new analog, 1 α ,25-dihydroxy-19-nor-vitamin D₃ (Ia) is as potent as 1 α ,25-dihydroxyvitamin D₃ in promoting the differentiation of leukemia cells. Thus in all three assays close to 90% of the cells are induced to differentiate by 1 α ,25-dihydroxyvitamin D₃ at a concentration of 1 x 10⁻⁷ molar, and the same degree of differentiation (i.e. 90, 84 and 90%) is achieved by the 19-nor analog (Ia).

Table 1			
Differentiation of HL-60 Cells			
1 α ,25-dihydroxyvitamin D ₃ (moles/liter)	% Differentiated Cells (mean \pm SEM)		
	NBT	NSE	PHAGO
1 x 10 ⁻⁷	86 \pm 2	89 \pm 1	87 \pm 3
1 x 10 ⁻⁸	60 \pm 2	60 \pm 3	64 \pm 2
1 x 10 ⁻⁹	33 \pm 2	31 \pm 2	34 \pm 1
1 α ,25-Dihydroxy-19-nor- vitamin D ₃ , (Ia) (moles/liter)			
2 x 10 ⁻⁷	94 \pm 2	95 \pm 3	94 \pm 2
1 x 10 ⁻⁷	90 \pm 4	84 \pm 4	90 \pm 4
5 x 10 ⁻⁸	72 \pm 3	73 \pm 3	74 \pm 3
1 x 10 ⁻⁸	61 \pm 3	60 \pm 3	56 \pm 1
1 x 10 ⁻⁹	32 \pm 1	31 \pm 1	33 \pm 1

In contrast to the preceding results, the new 19-nor analog (Ia) exhibits no activity in an assay measuring the calcification of bone, a typical response elicited by vitamin D compounds. Relevant data, representing the

results of an assay comparing the bone calcification activity in rats of 1 α ,25-dihydroxyvitamin D₃ and 1 α ,25-dihydroxy-19-nor-vitamin D₃ (Ia), are summarized in Table 2. This assay was conducted according to the procedure described by Tanaka *et al.*, Endocrinology 92, 417 (1973).

The results presented in Table 2 show the expected bone calcification activity of 1 α ,25-dihydroxyvitamin D₃ as reflected by the increase in percent bone ash, and in total ash at all dose levels. In contrast, the 19-nor analog Ia exhibits no activity at all three dose levels, when compared to the vitamin D-deficient (-D) control group.

Table 2
Calcification Activity

Compound	Amount Administered* (pmoles/day/7 days)	% Ash (mean \pm SEM)	Total Ash (mg) (mean \pm SEM)
-D (control)	0	19 \pm 0.8	23 \pm 1.2
1 α ,25-dihydroxy- vitamin D ₃	32.5	23 \pm 0.5	34 \pm 1.6
	65.0	26 \pm 0.7	36 \pm 1.1
	325.0	28 \pm 0.9	40 \pm 1.9
1 α ,25-dihydroxy-19- nor-vitamin D ₃ (Ia)	32.5	22 \pm 0.9	28 \pm 1.6
	65.0	19 \pm 1.5	28 \pm 3.4
	325.0	19 \pm 1.2	30 \pm 2.4

* Each assay group comprised 6 rats, receiving the indicated amount of test compound by intraperitoneal injection daily for a period of seven days.

Thus the new 19-nor analog shows a selective activity profile combining high potency in inducing the differentiation of malignant cells with very low or no bone calcification activity. The compounds of this novel structural class, therefore, can be useful as therapeutic agents for the treatment of malignancies. Because the differentiative activity of vitamin D compounds on keratinocytes of skin (Smith *et al.*, J. Invest. Dermatol. 86, 709, 1986; Smith *et al.*, J. Am. Acad. Dermatol. 19, 516, 1988) is believed to be an indication of successful treatment of psoriasis (Takamoto *et al.*, Calc. Tissue Int. 39, 360, 1986), these compounds should prove useful in treating this and other skin disorders characterized by proliferation of undifferentiated skin cells. These compounds should also find use in the suppression of parathyroid tissue, as for example, in cases of secondary hyperparathyroidism found in renal disease (Slatopolsky *et al.*, J. Clin. Invest. 74, 2136, 1984).

For treatment purposes, the novel compounds of this invention can be formulated in a solid or liquid vehicle ingestible by, and non toxic to, mammals, for example as solutions in innocuous solvents or as emulsions, suspensions or dispersions in suitable innocuous solvents or carriers, or as pills, tablets or capsules, containing solid carriers according to conventional methods known in the art. Accordingly the present invention provides a pharmaceutical composition which comprises at least one compound of this invention together with a pharmaceutically acceptable excipient. For topical applications or administrations the compounds are advantageously formulated as creams or ointments or similar vehicle suitable for topical applications. Any such formulations may also contain other pharmaceutically-acceptable and non-toxic excipients such as stabilizers, antioxidants, binders, coloring agents or emulsifying or taste-modifying agents.

The compounds are advantageously administered by injection (for parenteral administration), or by intra-

or intravenous infusion of suitable sterile solutions, or in the form of oral doses (for oral administration) via the alimentary canal, or topically in the form of ointments, lotions, or in suitable transdermal patches. For the treatment of malignant diseases, the 19-nor-vitamin D compounds of this invention should be administered to subjects in dosages sufficient to inhibit the proliferation of malignant cells and induce their differentiation into normal monocyte-macrophages. Similarly, for the treatment of psoriasis, the compounds may be administered orally or topically in amounts sufficient to arrest the proliferation of undifferentiated keratinocytes, and in the treatment of hyperparathyroidism, the compounds should be administered in dosages sufficient to suppress parathyroid activity, so as to achieve parathyroid hormone levels in the normal range. Suitable dosage amounts are from 1 to 500 µg of compound per day, such dosages being adjusted, depending on diseases to be treated, its severity and the response or condition of the subject as well-understood in the art. Typically a composition contains, in a single dosage form, from 0.5 µg to 50 µg of the compound.

This invention is more specifically described by the following illustrative examples. In these examples specific products identified by Roman numerals and letters, i.e. Ia, Ib, ..., IIa, IIb, ..., etc. refer to the specific structures and side chain combinations identified in the preceding description.

Example 1

Preparation of 1α,25-dihydroxy-19-nor-vitamin D₃ (Ia)

(a) 1α,25-Dihydroxy-3,5-cyclovitamin D₃ 1-acetate, 6-methyl ether (b): Using 25-hydroxyvitamin D₃ (IIa) as starting material, the known 1α,25-dihydroxy-3,5-cyclovitamin D₃ derivative IIIa (X=H) was prepared according to published procedures (DeLuca et al., U.S. Patent 4, 195,027 and Paaren et al., J. Org. Chem. 45, 3252 (1980)). This product was then acetylated under standard conditions to obtain the corresponding 1-acetate derivative IIIa (X=Ac).

(b) 10,19-Dihydro-1α,10,19,25-tetrahydroxy-3,5-cyclovitamin D₃ 1-acetate, 6-methyl ether (IVa): Intermediate IIIa (X=Ac) was treated with a slight molar excess of osmium tetroxide in pyridine according to the general procedure described by Paaren et al. (J. Org. Chem. 48, 3819 (1983)) to obtain the 10,19-dihydroxylated derivative IVa. Mass spectrum m/z (relative intensity), 506 (M⁺, 1), 488 (2), 474 (40), 425 (45), 396 (15), 285 (5), 229 (30), 133 (45), 59 (80), 43 (100). ¹H NMR (CDCl₃) δ 0.52 (3H, s, 18-CH₃), 0.58 (1H, m, 3-H), 0.93 (3H, d, J=6.1 Hz, 21-CH₃), 1.22 (6H, s, 26-CH₃ and 27-CH₃), 2.10 (3H, s, COCH₃), 3.25 (3H, s, 6-OCH₃), 3.63 (2H, m, 19-CH₂), 4.60 (1H, d, J=9.2 Hz, 6-H), 4.63 (1H, dd, 1β-H), 4.78 (1H, d, J=9.2 Hz, 7-H).

(c) 1α,25-Dihydroxy-10-oxo-3,5-cyclo-19-nor-vitamin D₃ 1-acetate, 6-methyl ether (Va): The 10,19-dihydroxylated intermediate IVa was treated with a solution of sodium metaperiodate according to the procedure given by Paaren et al. (J. Org. Chem. 48, 3819, 1983) to produce the 10-oxo-cyclovitamin D derivative (Va, X=Ac). Mass spectrum m/z (relative intensity) 442 (M⁺-MeOH) (18), 424 (8), 382 (15), 364 (35), 253 (55), 225 (25), 197 (53), 155 (85), 137 (100). ¹H NMR (CDCl₃) δ 0.58 (3H, s, 18-CH₃), 0.93 (3H, d, J=6.6 Hz, 21-CH₃), 1.22 (6H, s, 26-CH₃ and 27-CH₃), 2.15 (s, 3-OCOCH₃), 3.30 (3H, s, 6-OCH₃), 4.61 (1H, d, J=9.1 Hz, 6-H), 4.71 (1H, d, J=9.6 Hz, 7-H), 5.18 (1H, m, 1β-H).

It has been found also that this diol cleavage reaction does not require elevated temperatures, and it is, indeed, generally preferable to conduct the reaction at approximately room temperature.

(d) 1α-Acetoxy-10,25-dihydroxy-3,5-cyclo-19-nor-vitamin D₃ 6-methyl ether (VIa, X=Ac, Y=OH): The 10-oxo derivative Va (X=Ac) (2.2 mg, 4.6 µmol) was dissolved in 0.5 ml of ethanol and to this solution 50 µl (5.3 µmol) of a NaBH₄ solution (prepared from 20 mg of NaBH₄, 4.5 ml water and 0.5 ml of 0.01 N NaOH solution) was added and the mixture stirred at 0°C for ca. 1.5 h, and then kept at 0°C for 16 h. To the mixture ether was added and the organic phase washed with brine, dried over MgSO₄, filtered and evaporated. The crude product was purified by column chromatography on a 15 x 1 cm silica gel column and the alcohol VIa (X=Ac, Y=OH) was eluted with ethyl acetate hexane mixtures to give 1.4 mg (3 µmol) of product. Mass spectrum m/z (relative intensity) 476 (M⁺) (1), 444 (85), 426 (18), 384 (30), 366 (48), 351 (21), 255 (35), 237 (48), 199 (100), 139 (51), 59 (58).

(e) 1α,25-Dihydroxy-19-nor-vitamin D₃ (Ia, X¹=X²=H): The 10-alcohol (VIa, X=Ac, Y=OH) (1.4 mg) was dissolved in 100 µl anhydrous CH₂Cl₂ and 10 µl (14 µmol) triethylamine solution [prepared from 12 mg (16 µl) triethylamine in 100 µl anhydrous CH₂Cl₂], followed by 7 µl (5.6 µmol) mesyl chloride solution (9 mg mesyl chloride, 6.1 µl, in 100 µl anhydrous CH₂Cl₂) added at 0°C. The mixture was stirred at 0°C for 2 h. The solvents were removed with a stream of argon and the residue (comprising compound VIa, X=Ac, Y=CH₃SO₂O-) dissolved in 0.5 ml of anhydrous tetrahydrofuran; 5 mg of LiAlH₄ was added at 0°C and the mixture kept at 0°C for 16 h. Excess LiAlH₄ was decomposed with wet ether, the mixture was washed with water and dried over MgSO₄, filtered and evaporated to give the 19-nor product VIa (X=Y=H). This product was dissolved in 0.5 ml of acetic acid and stirred at 55°C for 20 min. The mixture was cooled,

ice water added and extracted with ether. The other phase was washed with cold 10% sodium bicarbonate solution, brine, dried over MgSO_4 , filtered and evaporated to give the expected mixture of 3-acetoxy-1 α -hydroxy- and 1 α -acetoxy-3-hydroxy isomers, which were separated and purified by HPLC (Zorbax Sil column, 6.4 x 25 cm, 2-propanol in hexane) to give about 70 μg each of compounds VIIa and XIIIa. UV (in EtOH) λ_{max} 242.5 (OD 0.72), 251.5 (OD 0.86), 260 (OD 0.57).

Both 19-nor-1,25-dihydroxyvitamin D_3 acetates VIIa and VIIIa were hydrolyzed in the same manner. Each of the monoacetates was dissolved in 0.5 ml of ether and 0.5 ml 0.1 N KOH in methanol was added. The mixture was stirred under argon atmosphere for 2 h. More ether was added and the organic phase washed with brine, dried over anhydrous MgSO_4 , filtered and evaporated. The residue was dissolved in a 1:1 mixture of 2-propanol and hexane and passed through a Sep Pak column and washed with the same solvent. The solvents were evaporated and the residue purified by HPLC (Zorbax Sil, 6.4 x 25 cm, 10% 2-propanol in hexane). The hydrolysis products of VIIa and VIIIa were identical and gave 66 μg of Ia ($\text{X}^1=\text{X}^2=\text{H}$). Mass spectrum (m/z relative intensity) 404 (M^+) (100), 386 (41), 371 (20), 275 (53), 245 (51), 180 (43), 135 (72), 133 (72), 95 (82), 59 (18), exact mass calcd. for $\text{C}_{28}\text{H}_{44}\text{O}_3$ 404.3290, found 404.3272. ^1H NMR (CDCl_3) δ 0.52 (3H, s, 18- CH_3), 0.92 (3H, d, $J=6.9$ Hz, 21- CH_3), 1.21 (6H, s, 26- CH_3 and 27- CH_3), 4.02 (1H, m, 3 α -H), 4.06 (1H, m, 1 β -H), 5.83 (1H, d, $J=11.6$ Hz, 7-H), 6.29 (1H, d, $J=10.7$ Hz, 6-H). UV (in EtOH), λ_{max} 243 (OD 0.725), 251.5 (OD 0.823), 261 (OD 0.598).

Example 2

Preparation of 1 α -hydroxy-19-nor-vitamin D_3 (Ib)

(a) With vitamin D_3 (IIb) as starting material, and utilizing the conditions of Example 1a, there is obtained known 1 α -hydroxy-3,5-cyclovitamin D_3 1-acetate, 6-methyl ether, compound IIIb ($\text{X}=\text{Ac}$).

(b) By subjecting intermediate IIIb ($\text{X}=\text{Ac}$), as obtained in Example 2a above to the conditions of Example 1b, there is obtained 10,19-dihydro-1 α ,10,19-trihydroxy-3,5-cyclovitamin D_3 1-acetate, 6-methyl ether IVb ($\text{X}=\text{Ac}$).

(c) By treatment of intermediate IVb ($\text{X}=\text{Ac}$) with sodium metaperiodate according to Example 1c above, there is obtained 1 α -hydroxy-10-oxo-3,5-cyclo-19-nor-vitamin D_3 1-acetate, 6-methyl ether Vb ($\text{X}=\text{Ac}$).

(d) Upon reduction of the 10-oxo-intermediate Vb ($\text{X}=\text{Ac}$) under the conditions of Example 1d above, there is obtained 1 α -acetoxy-10-hydroxy-3,5-cyclo-19-nor-vitamin D_3 6-methyl ether VIb ($\text{X}=\text{Ac}$, $\text{Y}=\text{OH}$).

(e) Upon processing intermediate VIb ($\text{X}=\text{Ac}$, $\text{Y}=\text{OH}$) through the procedure given in Example 1e above; there is obtained 1 α -hydroxy-19-nor-vitamin D_3 (Ib, $\text{X}^1=\text{X}^2=\text{H}$).

Example 3

Preparation of 1 α ,25-dihydroxy-19-nor-vitamin D_2

(a) Utilizing 25-hydroxyvitamin D_2 (IIc) as starting material and experimental conditions analogous to those of Example 1a, there is obtained 1 α ,25-dihydroxy-3,5-cyclovitamin D_2 1-acetate, 6-methyl ether, compound IIIc ($\text{X}=\text{Ac}$).

(b) Subjecting intermediate IIIc ($\text{X}=\text{Ac}$), as obtained in Example 3a above, to the reaction conditions of Example 1b, provides 10,19-dihydro-1 α ,10,19,25-tetrahydroxy-3,5-cyclovitamin D_2 1-acetate, 6-methyl ether, IVc ($\text{X}=\text{Ac}$).

(c) By treatment of intermediate IVc ($\text{X}=\text{Ac}$) with sodium metaperiodate according to general procedures of Example 1c above, there is obtained 1 α ,25-dihydroxy-10-oxo-3,5-cyclo-19-nor-vitamin D_2 1-acetate, 6-methyl ether Vc ($\text{X}=\text{Ac}$).

(d) Upon reduction of the 10-oxo-intermediate Vc ($\text{X}=\text{Ac}$) under conditions analogous to those of Example 1d above, there is obtained 1 α -acetoxy-10,25-dihydroxy-3,5-cyclo-19-nor-vitamin D_2 6-methyl ether VIc ($\text{X}=\text{Ac}$, $\text{Y}=\text{OH}$).

(e) Upon processing intermediate VIc ($\text{X}=\text{Ac}$, $\text{Y}=\text{OH}$) through the procedural steps given in Example 1e above, there is obtained 1 α ,25-dihydroxy-19-nor-vitamin D_2 (Ic, $\text{X}^1=\text{X}^2=\text{H}$).

Example 4

Preparation of 1 α -hydroxy-19-nor-vitamin D_2

(a) With vitamin D_2 (IId) as starting material, and utilizing the conditions of Example 1a, there is obtained known 1 α -hydroxy-3,5-cyclovitamin D_2 1-acetate, 6-methyl ether, compound IIId ($\text{X}=\text{Ac}$).

(b) By subjecting intermediate IIId ($\text{X}=\text{Ac}$), as obtained in Example 4a above to the conditions of Example 1b, there is obtained 10,19-dihydro-1 α ,10,19-trihydroxy-3,5-cyclovitamin D_2 1-acetate, 6-methyl ether,

IVd (X=Ac).

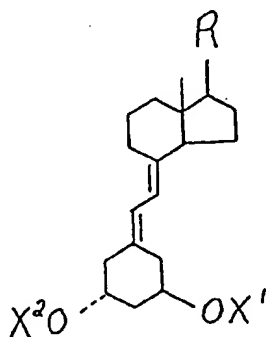
(c) By treatment of intermediate IVb (X=Ac) with sodium metaperiodat according to Example 1c above, there is obtained 1 α -hydroxy-10-oxo-3,5-cyclo-19-nor-vitamin D₂ 1-acetat, 6-methyl ether, Vd (X=Ac).

(d) Upon reduction of the 10-oxo-intermediate Vd (X=Ac) under the conditions of Example 1d above, there is obtained 1 α -acetoxy-10-hydroxy-3,5-cyclo-19-nor-vitamin D₂ 6-methyl ether, VId (X=Ac, Y=OH).

(e) Upon processing intermediate VId (X=Ac, Y=OH) through the procedure given in Example 1e above, there is obtained 1 α -hydroxy-19-nor-vitamin D₂ (Id, X¹=X²=H).

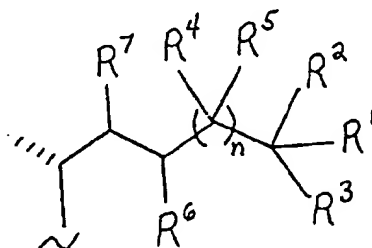
Claims

1. A compound having the formula:



where X¹ and X² are each independently hydrogen, aliphatic acyl of 1 to 5 carbon atoms, aromatic acyl or alkylsilyl or alkoxyalkyl wherein said "alkyl" has 1 to 5 carbon atoms, and R is a side chain known for vitamin D-type compounds:

2. A compound according to claim 1 wherein R is hydroxyalkyl of 1 to 5 carbon atoms, fluoroalkyl of 1 to 5 carbon atoms or a side chain of the formula:



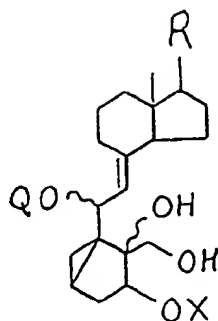
wherein R¹ represents hydrogen, hydroxy or O-acyl, R² and R³ are each independently alkyl, hydroxyalkyl or fluoroalkyl, or, when taken together represent the group

-- (CH₂)_m -- where m is an integer from 2 to 5, R⁴ is hydrogen, hydroxy, fluorine, O-acyl, alkyl, hydroxyalkyl or fluoroalkyl, R⁵ is hydrogen, fluorine, alkyl, hydroxyalkyl or fluoroalkyl, or R⁴ and R⁵ taken together represent double-bonded oxygen, R⁶ and R⁷ are each independently hydrogen, hydroxy, O-acyl, fluorine or alkyl, or R⁶ and R⁷ taken together form a carbon-carbon double bond, and n is an integer from 1 to 5 and wherein the carbon at any one of positions 20, 22 or 23 in the side chain may be replaced by an O, S, or N atom and wherein said "alkyl" has 1 to 5 carbon atoms and said "acyl" is aliphatic acyl of 1 to 5 carbon atoms or aromatic acyl.

3. A compound according to claim 1 wherein X¹ and X² are both hydrogen, R¹ is hydroxy, R² and R³ are each independently methyl, trifluoromethyl, ethyl or propyl, R⁶ and R⁷ are both hydrogen, or together form a carbon-carbon double bond, R⁴ and R⁵ are both hydrogen and n is 1, 2 or 3.

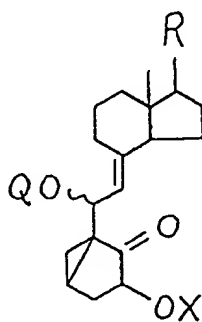
4. 1 α ,25-Dihydroxy-19-nor-vitamin D₃.

5. 1α -Hydroxy-19-nor-vitamin D_3 .
6. $1\alpha,25$ -Dihydroxy-19-nor-vitamin D_2 .
- 5 7. 1α -Hydroxy-19-nor-vitamin D_2 .
8. 1α -Hydroxy-19-nor-24 epi-vitamin D_2 .
9. $1\alpha,25$ -Dihydroxy-19-nor-24 epi-vitamin D_2 .
- 10 10. A compound having the formula:



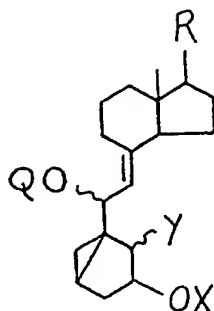
wherein R is as defined in Claim 1, Q represents alkyl and X is hydrogen, acyl, alkylsilyl or alkoxyalkyl, wherein said "alkyl" has 1 to 5 carbon atoms and said "acyl" is aliphatic acyl of 1 to 5 carbon atoms or aromatic acyl.

11. A compound having the formula:



wherein R is as defined in Claim 1, Q represents alkyl of 1 to 5 carbon atoms and X is as defined in Claim 10.

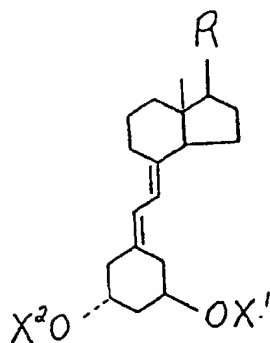
- 12. A compound having the formula:**



- wherein R is as defined in Claim 1, Q and X are as defined in claim 10, and Y is hydroxy, hydrogen or protected hydroxy where the protecting group is acyl, alkylsilyl or alkoxyalkyl, wherein said "alkyl" has 1 to 5 carbon atoms and said "acyl" is aliphatic acyl of 1 to 5 carbon atoms or aromatic acyl.
13. A pharmaceutical composition which comprises at least one compound as claimed in any one of claims 1 to 9 together with a pharmaceutically acceptable excipient.
 14. A composition according to claim 13 wherein the compound is in a solid or liquid vehicle ingestible by, and non-toxic to, mammals.
 15. A composition according to claim 13 or 14 wherein the compound is 1 α ,25-hydroxy-19-nor-vitamin D₃, 1 α -hydroxy-19-nor-vitamin D₃, 1 α ,25-dihydroxy-19-nor-vitamin D₂ or 1 α -hydroxy-19-nor-vitamin D₂.
 16. A composition according to any one of claims 13 to 15 which contains, in a single dosage form, from 0.5 μ g to 50 μ g of the compound.
 17. A composition according to any one of claims 13 to 16 which is suitable for topical administration.
 18. A composition according to any one of claims 13 to 16 which is suitable for parenteral administration.
 19. A composition according to any one of claims 13 to 16 which is suitable for oral administration.
 20. A compound as defined in any one of claims 1 to 9 for inducing cell differentiation in malignant cells.
 21. A compound as defined in any one of claims 1 to 9 for inducing cell differentiation in leukemia cells.
 22. A compound as defined in any one of claims 1 to 9 for treating a proliferative skin disorder in a mammal.
 23. A compound as defined in any one claims 1 to 9 for treating psoriasis.
 24. A compound as defined in any one of claims 1 to 9 for treating primary or secondary hyperparathyroidism.
 25. A compound as defined in any one of claims 1 to 9 for treating a neoplastic disease.
 26. A process for preparing a compound having the formula:

5

10



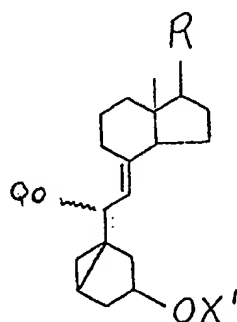
15

where X¹, X² and R are as defined in any one of Claims 1 to 3 which comprises solvolysing the 1 α -hydroxy-10-deoxy cyclovitamin D compound having the formula:

20

25

30



wherein Q is alkyl of 1 to 5 carbon atoms.

35

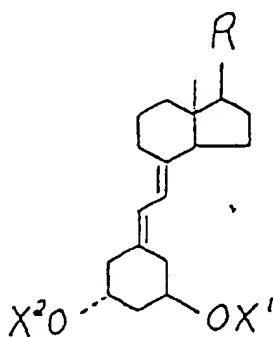
Patentansprüche

1. Verbindung der Formel

40

45

50



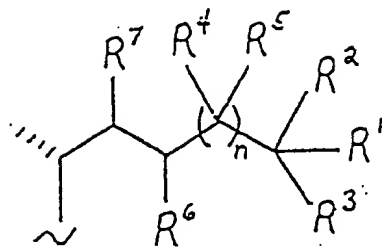
55

worin X¹ und X² unabhängig voneinander Wasserstoff, aliphatisches Acyl mit 1 bis 5 Kohlenstoffatomen, aromatisches Acyl oder Alkylsilyl oder Alkoxyalkyl, worin "Alkyl" 1 bis 5 Kohlenstoffatome besitzt, bedeuten, und R eine für Verbindungen des Vitamin-D-Typs bekannte Seitenkette ist.

2. Verbindung nach Anspruch 1, dadurch gekennzeichnet, daß R Hydroxyalkyl mit 1 bis 5 Kohlenstoffatomen, Fluoralkyl mit 1 bis 5 Kohlenstoffatomen oder eine Seitenkette der Formel ist:

5

10



15

20

worin R1 Wasserstoff, Hydroxy oder O-Acyl bedeutet, R2 und R3 unabhängig voneinander Alkyl, Hydroxyalkyl oder Fluoralkyl bedeuten oder zusammengekommen die Gruppe $-(CH_2)_m-$ darstellen, worin m eine ganze Zahl von 2 bis 5, R4 Wasserstoff, Hydroxy, Fluor, O-Acyl, Alkyl, Hydroxyalkyl oder Fluoralkyl ist, R5 Wasserstoff, Fluor, Alkyl, Hydroxyalkyl oder Fluoralkyl ist, oder R4 und R5 zusammen einen doppelt gebundenen Sauerstoff bedeuten, R6 und R7 unabhängig voneinander Wasserstoff, Hydroxy, O-Acyl, Fluor oder Alkyl sind, oder R6 und R7 zusammen eine Kohlenstoff-Kohlenstoff-Doppelbindung bilden, und n eine ganze Zahl von 1 bis 5 ist, und worin das Kohlenstoffatom an irgendeiner der Stellungen 20, 22 oder 23 in der Seitenkette durch ein O, S oder N-Atom ersetzt sein kann, und worin "Alkyl" 1 bis 5 Kohlenstoffatome besitzt, und "Acyl" ein aliphatisches Acyl mit 1 bis 5 Kohlenstoffatomen oder ein aromatisches Acyl ist.

25

3. Verbindung nach Anspruch 1, dadurch gekennzeichnet, daß X1 und X2 beide Wasserstoff sind, R1 Hydroxy ist, R2 und R3 unabhängig voneinander Methyl, Trifluormethyl, Ethyl oder Propyl bedeuten, R6 und R7 beide Wasserstoff sind, oder zusammen eine Kohlenstoff-Kohlenstoff-Doppelbindung bilden, R4 und R5 beide Wasserstoff sind, und n 1, 2 oder 3 ist.

30

4. 1 α ,25-Dihydroxy-19-nor-Vitamin-D3

5. 1 α -Hydroxy-19-nor-Vitamin-D3

6. 1 α ,25-Dihydroxy-19-nor-Vitamin-D2

7. 1 α -Hydroxy-19-nor-Vitamin-D2

35

8. 1 α -Hydroxy-19-nor-24 epi-Vitamin-D2

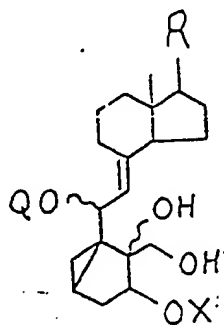
9. 1 α ,25-Dihydroxy-19-nor-24 epi-Vitamin-D2

40

10. Verbindung der Formel

45

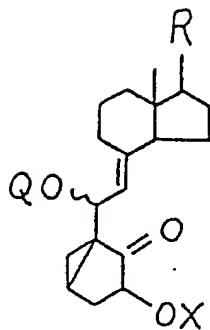
50



55

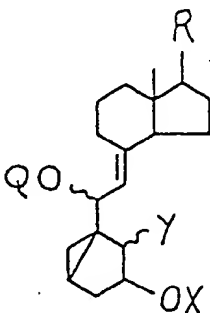
worin R die im Anspruch 1 angegebene Bedeutung besitzt, Q Alkyl bedeutet und X Wasserstoff, Acyl, Alkylsilyl oder Alkoxyalkyl ist, und worin "Alkyl" 1 bis 5 Kohlenstoffatome besitzt, und "Acyl" ein aliphatisches Acyl mit 1 bis 5 Kohlenstoffatomen oder ein aromatisches Acyl ist.

11. Verbindung der Formel:



15 worin R die im Anspruch 1 angegebene Bedeutung besitzt, Q Alkyl mit 1 bis 5 Kohlenstoffatomen bedeutet, und X die im Anspruch 10 angegebene Bedeutung besitzt.

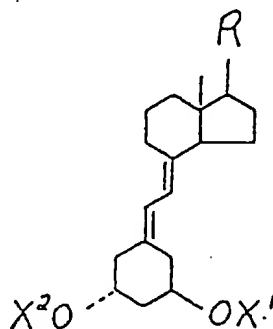
12. Verbindung der Formel:



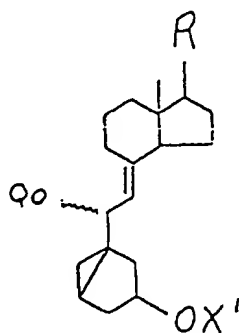
35 worin R die im Anspruch 1 angegebene Bedeutung besitzt, Q und X die im Anspruch 10 angegebene Bedeutung besitzen und Y Hydroxy, Wasserstoff oder eine geschützte Hydroxygruppe ist, worin die Schutzgruppe Acyl, Alkylsilyl oder Alkoxyalkyl ist, und worin "Alkyl" 1 bis 5 Kohlenstoffatome besitzt und "Acyl" ein aliphatisches Acyl mit 1 bis 5 Kohlenstoffatomen oder ein aromatisches Acyl ist.

13. Pharmazeutische Zusammensetzung, dadurch gekennzeichnet, daß sie mindestens eine Verbindung nach einem der Ansprüche 1 bis 9 zusammen mit einem pharmazeutisch annehmbaren Träger umfaßt.
- 40 14. Zusammensetzung nach Anspruch 13, dadurch gekennzeichnet, daß die Verbindung in einem festen oder flüssigen Träger, der von Säugern mit der Nahrung aufnehmbar und für sie nicht toxisch ist, vorhanden ist.
- 45 15. Zusammensetzung nach Anspruch 13 oder 14, dadurch gekennzeichnet, daß die Verbindung 1 α ,25-Hydroxy-19-nor-Vitamin-D3, 1 α -Hydroxy-19-nor-Vitamin-D3, 1 α ,25-Dihydroxy-19-nor-Vitamin-D2 oder 1 α -Hydroxy-19-nor-Vitamin-D2 ist.
- 50 16. Zusammensetzung nach einem der Ansprüche 13 bis 15, dadurch gekennzeichnet, daß sie 0.5 μ g bis 50 μ g der Verbindung in einer Einzeldosisform enthält.
17. Zusammensetzung nach einem der Ansprüche 13 bis 16, dadurch gekennzeichnet, daß sie für eine topische Verabreichung geeignet ist.
18. Zusammensetzung nach einem der Ansprüche 13 bis 16, dadurch gekennzeichnet, daß sie für eine parenterale Verabreichung geeignet ist.
- 55 19. Zusammensetzung nach einem der Ansprüche 13 bis 16, dadurch gekennzeichnet, daß sie für orale Verabreichung geeignet ist.

20. Verbindung nach einem der Ansprüche 1 bis 9 zur Induzierung der Zelldifferenzierung in malignen Zellen.
21. Verbindung nach einem der Ansprüche 1 bis 9 zur Induzierung der Zelldifferenzierung in Leukämiezellen.
22. Verbindung nach einem der Ansprüche 1 bis 9 zur Behandlung einer sich stark vermehrenden Hautkrankheit in einem Säuger.
23. Verbindung nach einem der Ansprüche 1 bis 9 zur Behandlung von Psoriasis.
24. Verbindung nach einem der Ansprüche 1 bis 9 zur Behandlung von primärem oder sekundärem Hyperparathyroidismus.
25. Verbindung nach einem der Ansprüche 1 bis 9 zur Behandlung einer neoplastischen Erkrankung.
26. Verfahren zur Herstellung einer Verbindung der Formel:



worin X1, X2 und R die in einem der Ansprüche 1 bis 3 angegebene Bedeutung besitzen, dadurch gekennzeichnet, daß man die 1 α -Hydroxy-10-deoxy Cyclovitamin-D-Verbindung der Formel:



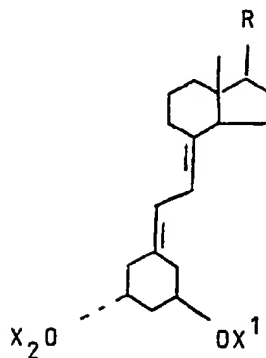
worin Q Alkyl mit 1 bis 5 Kohlenstoffatomen bedeutet, einer Solvolyse unterwirft.

Revendications

1. Composé ayant la formule :

5

10



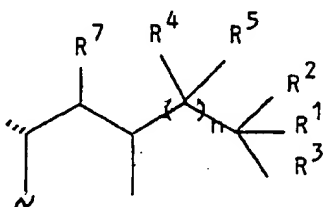
15

dans laquelle X¹ et X² représentent, indépendamment l'un de l'autre, l'hydrogène, un acyle aliphatique ayant 1 à 5 atomes de carbone, un acyle aromatique ou un alkylsilyle ou un alcoxyalkyle dans lesquels le radical alkyle a 1 à 5 atomes de carbone, et R est une chaîne latérale connue pour les composés du type vitamine D.

20

2. Composé selon la revendication 1, caractérisé en ce que R représente un radical hydroxyalkyle ayant 1 à 5 atomes de carbone, fluoroalkyle ayant 1 à 5 atomes de carbone ou une chaîne latérale de formule :

25



30

dans laquelle R¹ représente l'hydrogène, un groupe hydroxy ou O-acyle, R² et R³, indépendamment l'un de l'autre, représentent un radical alkyle, hydroxyalkyle ou fluoroalkyle, ou, pris ensemble, représentent le groupe -(CH₂)_m - où m est un nombre entier de 2 à 5, R⁴ représente l'hydrogène, un groupe hydroxy, le fluor, un radical O-acyle, alkyle, hydroxyalkyle ou fluoroalkyle, R⁵ représente l'hydrogène, le fluor, un radical alkyle, hydroxyalkyle ou fluoroalkyle, ou R⁴ et R⁵ pris ensemble représentent une double liaison oxygène, R⁶ et R⁷ représentent indépendamment l'un de l'autre, l'hydrogène, un groupe hydroxy, le fluor, un radical O-acyle ou alkyle, ou R⁶ et R⁷ pris ensemble forment une double liaison carbone-carbone, et n est un nombre entier de 1 à 5, et, dans laquelle, le carbone dans l'une quelconque des positions 20, 22 ou 23 de la chaîne latérale peut être remplacé par un atome O, S ou N et, dans laquelle, le radical alkyle a 1 à 5 atomes de carbone et le radical acyle est un acyle aliphatique ayant 1 à 5 atomes de carbone ou un acyle aromatique.

35

40

45

3. Composé selon la revendication 1, caractérisé en ce que X¹ et X² représentent tous deux l'hydrogène, R¹ est un groupe hydroxy, R₂ et R₃ représentent, indépendamment l'un de l'autre, le radical méthyle, trifluorométhyle, éthyle ou propyle, R⁶ et R⁷ représentent tous deux l'hydrogène, ou forment ensemble une double liaison carbone-carbone, R⁴ et R⁵ représentent tous deux l'hydrogène et n vaut 1, 2 ou 3.

50

4. La 1α, 25-Dihydroxy-19-nor-vitamine D₃.

5. La 1α-Hydroxy-19-nor-vitamine D₃.

6. La 1α,25-Dihydroxy-19-nor-vitamine D₂.

55

7. La 1α-Hydroxy-19-nor-vitamin D₂.

8. La 1α-Hydroxy-19-nor-24 epi-vitamine D₂.

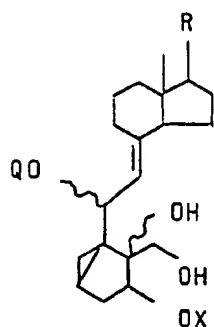
9. La 1 α ,25-Dihydroxy-19-nor-24 epi-vitamine D₂.

10. Composé ayant la formule :

5

10

15



20

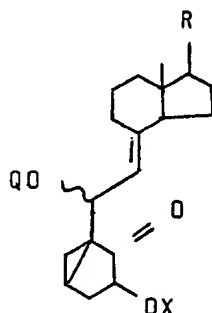
dans laquelle R est tel que défini dans la revendication 1, Q représente un radical alkyle et X représente l'hydrogène, un radical acyle, alkylsilyle ou alcoxyalkyle, dans laquelle ledit radical alkyle a 1 à 5 atomes de carbone et ledit radical acyle est un acyle aliphatique ayant 1 à 5 atomes de carbone ou un acyle aromatique.

11. Composé ayant la formule :

25

30

35



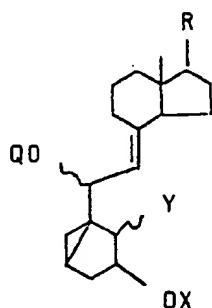
40

dans laquelle R est tel que défini dans la revendication 1, Q représente un radical alkyle ayant 1 à 5 atomes de carbone et X est tel que défini dans la revendication 10.

12. Composé ayant la formule :

45

50

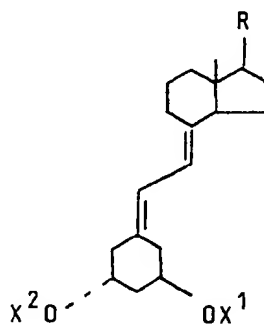


55

dans laquelle R est tel que défini dans la revendication 1, Q et X sont tels que définis dans la revendication 10, et Y représente un groupe hydroxy, l'hydrogène ou un groupe hydroxy protégé pour lequel le groupe protecteur est un radical acyl, alkylsilyle ou alcoxyalkyl, dans laquelle ledit radical alkyl a 1 à 5 atomes de carbone et ledit radical acyle est un acyl aliphatique ayant 1 à 5 atomes de carbone ou un

acyle aromatique.

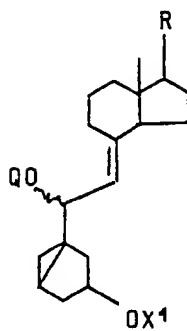
13. Composition pharmaceutique qui comprend au moins un composé tel que défini dans l'un quelconque des revendications 1 à 9 ainsi qu'un excipient pharmaceutiquement acceptable.
14. Composition selon la revendication 13, caractérisée en ce que le composé est dans un véhicule solide ou liquide ingérable par et non toxique vis-à-vis des mammifères.
15. Composition selon la revendication 13 ou 14, caractérisée en ce que le composé est la 1 α ,25-hydroxy-19-nor-vitamine D₃, la 1 α -hydroxy-19-nor-vitamine D₃, la 1 α ,25-dihydroxy-19-nor-vitamine D₂ ou la 1 α -hydroxy-19-nor-vitamine D₂.
16. Composition selon l'une quelconque des revendications 13 à 15, caractérisée en ce qu'elle contient, en une seule forme de dosage, 0,5 à 50 μ m du composé.
17. Composition selon l'une quelconque des revendications 13 à 16 convenant à l'administration par voie topique.
18. Composition selon l'une quelconque des revendications 13 à 16 convenant à l'administration parentérale.
19. Composition selon l'une quelconque des revendications 13 à 16 convenant à l'administration orale.
20. Composé selon l'une quelconque des revendications 1 à 9 pour provoquer une différenciation cellulaire dans les cellules malignes.
21. Composé selon l'une quelconque des revendications 1 à 9 pour provoquer une différenciation cellulaire dans les cellules de la leucémie.
22. Composé selon l'une quelconque des revendications 1 à 9 pour le traitement de maladies prolifératives de la peau chez un mammifère.
23. Composé selon l'une quelconque des revendications 1 à 9 pour le traitement du psoriasis.
24. Composé selon l'une quelconque des revendications 1 à 9 pour le traitement de l'hyperparathyroïdisme primaire ou secondaire.
25. Composé selon l'une quelconque des revendications 1 à 9 pour le traitement d'une maladie néoplasique.
26. Procédé pour la préparation de composé ayant la formule :



dans laquelle X¹, X² et R sont tels que définis dans l'une quelconque des revendications 1 à 3 comprenant la solvolysé du composé 1-hydroxy-10-déoxy cyclovitamine D ayant la formule :

5

10



15

dans laquelle Q est un radical alkyle ayant 1 à 5 atomes de carbone.

20

25

30

35

40

45

50

55